# Major Kidney Clinical Research Studies and Projects Inventory

# African American Study of Kidney Disease and Hypertension (AASK) Clinical Trial and Cohort Study

## 1. Administrative Data

(a) Name of study/research project and acronym:

African American Study of Kidney Disease and Hypertension (AASK)

(b) Type of study/research project (randomized clinical trial, epidemiological study, database, etc.):

Randomized clinical trial followed by a cohort study

(c) Funding status (currently funded, study/project completed):

Randomized clinical trial is completed; cohort study is currently funded.

(d) Recruitment status (recruitment completed, currently recruiting):

Recruitment for cohort study is nearly completed, but only patients who were previously in the randomized trial are eligible.

(e) For studies/project currently recruiting, indicate total sample size/ number currently enrolled and anticipated period of recruitment:

For the randomized trial, we randomized 1,043 patients.

For the cohort study, we have 663 patients, and we anticipate our total will be 670 to 675. Of the patients who were in the trial, 790 appear to be alive and not on dialysis.

(f) Data coordinating center principal investigator contact information (mailing address, phone, fax, and e-mail address)

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(g) Number of recruiting sites, list of principal investigators at recruiting sites and contact information as in (f) above

21 recruiting sites. See Appendix A.

(h) List of Principal Investigators at central laboratories/facilities (identify type of central facility) and contact information as in (f) and (g) above

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(i) Roster of Data and Safety Monitoring Board/Scientific Advisory Committee or other oversight committee(s):

See Appendix B

(j) Private sector support (type of support, e.g., financial, donation of drugs/placebo, etc.)

For the cohort study, King Pharmaceuticals is donating drugs and money.

## 2. Study Design

*Design paper for the trial:*

Gassman J, Greene T, Wright J, Agodoa L, Bakris G et al. Design and statistical aspects of the African American Study of kidney disease and hypertension (AASK). See Appendix C.

*Results paper for the trial:*

Wright JT, Bakris G, Greene G, Agodoa L, Appel L et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease. *JAMA*, 2002. 288;19:2421-2431.

*Design paper for the cohort study:*

Appel L, Middleton J, Miller E, Lipkowitz M, Norris K et al. The rationale and design of the AASK Cohort Study. See Appendix D.

## 3. Data and Biological Sample Resources

(a) Biological samples collected in ongoing studies/research projects (specify the type of sample, e.g., blood, urine, etc., the amount, and the point in the study when samples were collected, e.g., baseline visit #1, baseline visit #2, follow-up visit #1; specify months after randomization/study entry):

*AASK Study:*

- Serum: In AASK, serum was collected twice during the Baseline period (at SV2 and G1). At the Safety Visit (FV0-1), serum was drawn to look at potassium and creatinine values since patients should have started the blinded

medications fairly recently. Serum was drawn at FV3-0 (K and Cr only), FV6-0 (K and Cr only) during the first year of enrolling. At FV12-0 and yearly a serum was drawn for full analysis and K and Cr were drawn every six months. Also, serum was collected if a potassium or serum creatinine action item was declared during follow-up.

- Urine: In AASK, urine was collected once in Baseline (B-1) and very six months during follow-up (FV6-0, Fy12, Fy18, Fy24, etc.). Urine was collected after a potential protein/creatinine action item for diabetic patients when indicated.

*Cohort Study:*

- DNA is collected on ESRD and non-ESRD patients.
- Serum is collected twice in baseline, and the serum creatinine is averaged (C0 and C0-l). Fasting and non-fasting samples are drawn during Baseline.
- Fasting (creatinine, lipids, glucose, insulin, routine chemistry, CBC) serum is drawn at C0 and annually. A non-fasting sample to look at serum creatinine is drawn at C6, C18, C30, C42, etc.
- Local blood samples are drawn at C0 and annually also.
- Fingernail samples are collected at C0 and annually.
- 24-hr urine specimen is collected at C0 and annually.

(b) Biological samples currently in storage from completed trials (grid showing sample collection time, type of sample, amount, and number of study participants sample was collected from, and physical location of where the samples are stored)

See Table 1 below.

| Table 1. AASK Study Biological Samples Currently in Storage | | | | |
|---|---|---|---|---|
| | **VIST** | **VISN** | **VISSEQ** | **Number** |
| **Buffy Coat** | G | 1 | 0 | 1530 |
| **Urine x 2 Each** | B | 1 | 0 | 2287 |
| | G | 1 | 0 | 5 |
| | FV | 2 | 0 | 1 |
| | FV | 3 | 0 | 1 |
| | FV | 6 | 0 | 11 |
| | FV | 12 | 0 | 859 |
| | FV | 18 | 0 | 1 |
| | FV | 24 | 0 | 604 |
| | FV | 36 | 0 | 399 |
| | FV | 48 | 0 | 153 |
| **Serum x 2 Each** | FV | 1 | 0 | 1 |
| | FV | 12 | 0 | 880 |
| | FV | 24 | 0 | 633 |
| | FV | 36 | 0 | 424 |
| | FV | 48 | 0 | 153 |
| | G | 1 | 0 | 1880 |

(c) Brief summary of typical informed consent provisions (template informed consent form acceptable), including major variables in participant consents, if applicable. For example, “use for other studies or not”, “allow genetic studies or not.” Does consent include use of samples in other studies that are not part of the main study?

Appendix E, cohort consent template, and Appendix F, cohort genetics consent template.

(d) Data collected (grid of data collection by time/clinic visit with specificity on the type of information collected, e.g., quality of life with SF-MOS 36, measurement of kidney function by GFR, serum creatinine measurement, etc.)

*Renal function:*

- In the trial only, iothalamate GFR every four months
- In the trial, serum creatinine every four months

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- In the cohort study, serum creatinine every six months

*Quality of life:*

- In the trial, quality of life every year.
- In the cohort study, quality of life every year.

*ECGs:*

- In the trial, every year
- In the cohort study, every two years

*Echos:*

- None in the trial
- In the cohort study, every two years

(e) Any provisions for distributing resources outside of the study. What is the sharing plan?

We have a protocol for this, Appendix G

**4. Ancillary Studies**

(a) Process and contact person (name, address, phone, fax, and e-mail address) for application to perform ancillary studies:

*Process:* Follow the protocol in Appendix G.

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(b) List of ancillary studies approved, completed, and ongoing (including source of funding and amount)

See Appendix H

**5. List of Publications and Presentations (full citations, also note manuscripts in progress)**

See Appendix I.

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# Appendix C. AASK Trial Design

## Design and Statistical Aspects of the African American Study of Kidney Disease and Hypertension (AASK)
**(in press at JASN)**

From the AASK Group, presented by Jennifer J. Gassman, Ph.D.[1], Tom Greene, Ph.D. [1], Jackson T. Wright, Jr., M.D., Ph.D.[4], Lawrence Agodoa, M.D.[2], George Bakris, M.D.[3] Gerald J. Beck, Ph.D. [1], Janice Douglas, M.D. [4], Ken Jamerson, M.D.[5], Julia Lewis, [6], Michael Kutner, Ph.D. [1], Otelio S. Randall, M.D.[7], and Shin-Ru Wang, M.S. [1]

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### Abstract

The African American Study of Kidney Disease and Hypertension (AASK) is a multi-center randomized clinical trial designed to test the effectiveness of three antihypertensive drug regimens and two levels of blood pressure control on the progression of hypertensive kidney disease. Participants include African American men and women aged 18 to 70 years who have hypertensive kidney disease and a glomerular filtration rate (GFR) between 20 and 65 ml/min/1.73 $m^2$. The three antihypertensive drug regimens include ramipril, an angiotensin-converting enzyme inhibitor (ACEI); amlodipine, a dihydropyridine calcium channel blocker (DHPCCB); or metoprolol, a beta blocker (BB), as initial therapy. The blood pressure control levels are a lower goal (Mean Arterial Pressure [MAP] $\leq$92 mmHg) and a usual goal (MAP between 102-107 mmHg inclusive). The primary outcome is rate of change in renal function as measured by GFR, assessed by $^{125}$I-iothalamate clearance. The main secondary patient outcome is a composite that includes the following events: (1) reduction in GFR by 50%, (2) end stage renal disease, or (3) death.

## Introduction

The African American Study of Kidney Disease and Hypertension (AASK) is a full-scale randomized clinical trial sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH). The AASK is investigating whether any of three blood pressure medication regimens or either of two levels of blood pressure control can slow the progression of kidney disease in patients with hypertensive nephrosclerosis. AASK has randomized 1,094 African Americans with hypertension and reduced renal function ($^{125}$I-iothalamate GFR 20 to 65 ml/min/l.73 $m^{2)}$ at 21 clinical centers in 13 states across the United States.

Hypertensive nephrosclerosis has been reported to be the second leading cause of renal failure in the United States and, until recently, the leading cause of renal failure, or end stage renal disease (ESRD), in African Americans (1,2). Over the past 20 years, new antihypertensive medications have contributed to lower rates of mortality and morbidity due to stroke and heart disease. However, the rate of ESRD due to hypertension has continued to increase and remains higher in African Americans than other subgroups in the United States (1,3). Although African Americans make up only 12% of the U.S. population, 28% of the patients on hemodialysis are African American, and African Americans develop ESRD (defined by the need for dialysis or transplantation) at a rate four times greater than that for Whites (4). It is not clear what accounts for increased susceptibility of African Americans to ESRD (5-11). It is not entirely explained by the higher prevalence of hypertension (12,13) or by socioeconomic factors in the African American population (14).

It has been demonstrated that long-term blood pressure control to recommended standards for controlling cardiovascular disease with conventional antihypertensive medications (including ganglionic blocking agents, reserpine, diuretics, vasodilators, and beta blockers) can help preserve renal function (15-21). However, large-scale trials in patients with hypertensive renal disease have generally not been designed to assess change in renal function in relation to blood pressure control and have relied on indirect estimates of GFR by serum creatinine concentration.

Two previous randomized trials (22, 23) have examined the effects of low blood pressure goals similar to the lower goal of the AASK on renal disease progression. The rationale for the lower blood pressure goal in the AASK was provided in part by a subgroup analysis of 53 African Americans in one of these trials, the Modification of Diet in Renal Disease (MDRD) Study, which suggested a benefit of the lower BP goal in African Americans (22, 24). However, the question of whether controlling blood pressure to levels below current standards further slows the progression of renal disease in patients with hypertension and renal insufficiency (25) has not been resolved. It is also unknown whether specific classes of antihypertensive medications are more effective in slowing renal disease progression in this population independent of their effects on blood pressure.

The AASK Pilot Study was conducted with 94 patients at 11 clinical centers in 1992-1993 (26). The full-scale AASK is being carried out in 21 clinical centers (see Appendix 1). The clinical centers include all four of the historically AA medical schools: Howard University, Martin Luther King-Drew Medical College, Meharry Medical College, and the Morehouse School of Medicine.

This report presents the design and statistical analysis plan for the full-scale phase of the AASK. Special attention is given to challenges for the analysis plan associated with the expectation of differences between short-term and long-term effects of the interventions.

## Methods

The AASK pilot study was conducted to document the feasibility of meeting the study objectives and to evaluate study procedures (26). Enrollment for the full-scale study began in March 1995, and 1,094 patients were randomized between June 1995 and September 1998 (27). Patients will continue to be followed through September 2001. In this 3 x 2 factorial trial, the three antihypertensive medication regimens begin with ramipril, an angiotensin converting enzyme inhibitor (ACEI); amlodipine, a dihydropyridine calcium channel blocker (DHPCCB), or metoprolol, a beta blocker (BB).

The two levels of blood pressure control are a usual goal (MAP 102-107 mmHg), which corresponds to a blood pressure of approximately 135/85 to 140/90 mmHg, or lower goal (MAP $\leq$92 mmHg), which corresponds to a blood pressure of approximately 115/80. Enrollment by randomized group is shown in Table 1. Fewer patients were enrolled into the DHPCCB group because, as described later, the anticipated hemodynamic effect of these agents on GFR increases the statistical power of comparisons of the DHPCCB group compared to the other treatment groups.

**Table 1. AASK Enrollment by Randomized Group**

| MAP Goal | Initial (Blinded) Therapy in Drug Regimen | | | |
|---|---|---|---|---|
| | ACE Inhibitor (ACEI) | Beta Blocker (BB) | Calcium Channel Blocker (DHPCCB) | TOTAL |
| **MAP $\leq$ 92** | 215 | 215 | 110 | 540 |
| **MAP 102-107** | 221 | 226 | 107 | 554 |
| **TOTAL** | 436 | 441 | 227 | 1094 |

The usual goal reflects good blood pressure control in an otherwise normal hypertensive population. The low goal of MAP $\leq$ 92 mm/Hg is a lower goal of unproven benefit. The lower limit of 102 in the usual goal provides a minimum targeted separation between the

two MAP groups of 10 mmHg, and is intended to facilitate separation in achieved blood pressure between the lower and usual blood pressure groups.

Investigators and participants are unblinded to the blood pressure group assignment. Patients are seen at least every other month, and blood pressures are measured at each visit using random zero sphygmomanometers. If a patient's MAP is more than 5 mmHg over goal on two consecutive visits, an extra visit is held.

**Antihypertensive Medications**

Animal data suggest that both ACEIs and CCBs may provide renoprotection independent of their effect on blood pressure (28, 29), and ACEIs have been shown to be renoprotective for patients with diabetic renal disease (30,31). BBs were selected as the reference to determine if ACEIs or DHPCCBs are renoprotective in African Americans with hypertensive nephrosclerosis, as there is less evidence for renoprotective effects of BBs than the other two agents. BBs also inhibit renin release and thereby lower intrarenal angiotensin II levels but to a lesser extent that ACEIs.

The AASK's intent is to test whether the randomized drug regimens containing ACEIs or CCBs better preserve renal function in African Americans with renal insufficiency attributed to hypertensive renal disease, independent of these drugs' effects on blood pressure. Patients are randomized to one of the three blinded, antihypertensive agents as a first step in a stepped-care regimen of hypertensive medication. At each visit, patients are prescribed either the low, medium, or high dose of their blinded antihypertensive medication. Staff members work to keep each patient's blood pressure within its assigned range by increasing the dose of the blinded medication to the highest level that does not put the patient below goal, by adding or changing doses of the stepped care regimens, or by using non-pharmacologic therapy. AASK medication masking is accomplished through a double-dummy system in which each patient takes one tablet (either BB or placebo) and one capsule (either an ACEI, DHPCCB, or placebo) each day.

The ACEI ramipril doses are 2.5 mg, 5 mg, or 10 mg and the BB metoprolol doses are 50 mg, 100 mg, or 200 mg. For the DHPCCB amlodipine, only two doses are used, but the blinding requires that doses of 5 mg, 5 mg, and 10 mg be considered low, medium, and high, respectively.

It was anticipated that additional antihypertensive medications would be required to achieve the blood pressure goals, especially the lower goal. The AASK stepped care system includes the following antihypertensive medication steps:

- Diuretics (preferably furosemide)
- Alpha-adrenoreceptor antagonists (preferably doxazosin)
- Centrally-acting Alpha II agonists (preferably clonidine)

- Vasodilators (preferably minoxidil or hydralazine)

The use of additional stepped-care antihypertensive medications in the three antihypertensive treatment arms was expected to be similar, though antihypertensive requirements were expected to be greater in the lower than usual blood pressure group. When clinically possible, the drugs are added step by step, with each prior step maximized before adding the next step. Study coordinators and a study-wide Adherence Committee work to promote adherence by counseling patients and providing feedback on blood pressure level attained and results of pill counting. Pill counts are done at each protocol visit.

## Eligibility and the Patient Timeline

African Americans between 18 and 70 years of age with presumed hypertensive chronic renal disease and $^{125}$I-iothalamate GFR between 20 and 65 ml/min/l.73 $m^2$ were eligible to enroll in the AASK. This GFR represents between a 33 percent to 80 percent decline from normal renal function. From the AASK pilot study, which included renal biopsies (26), it was determined that hypertensive nephrosclerosis could be confirmed in this population based on clinical grounds. Thus, biopsy evidence of hypertensive nephrosclerosis was not sought for the full-scale study. Other eligibility and exclusion criteria are shown in Table 2.

**Table 2. AASK Inclusion and Exclusion Criteria**

**Inclusion Criteria**

1. African-American men and women (including Black persons born in the Caribbean, Africa, Canada, etc.) age 18-70 years. Each center will attempt to include equal numbers of men and women, at least one third of each.

2. Hypertension is defined as a sitting diastolic blood pressure of 95 mmHg or more. The average of the last two of three consecutive readings on a random zero sphygmomanometer machine at any visit is the level used. Hypertensive participants on antihypertensive therapy at Baseline need only one qualifying clinic visit. Those not currently on medications at Baseline must qualify on each of two consecutive clinic visits.

3. Reduced renal function, defined as a pre-randomization (G1 visit) $^{125}$I-iothalamate glomerular filtration rate between 20-65 ml/min/1.73$m^2$.

4. Willingness and ability to cooperate with the protocol.

**Exclusion Criteria**

1. History of malignant or accelerated hypertension within six months before study entry; previous chronic peritoneal or hemodialysis or renal transplantation.

2. Known secondary causes of hypertension.

3. Any known history of diabetes mellitus type I and II, or fasting (8-12 hrs.) glucose > 140 mg/dl on two occasions, or glucose > 200 mg/dl on one occasion prior to randomization.

4. A ratio of urinary protein (mg/dl) to creatinine (mg/dl) exceeding 2.5 in a 24-hour urine sample collected shortly before the initial GFR visit. (This ratio is used as an estimate of > 2.5 g/day proteinuria without needing to factor for validity of the collection.)

5. Clinical or renal biopsy evidence of any renal disease other than hypertensive nephrosclerosis. Persons with arteriographically documented renal arterial atherosclerotic disease less than 50% stenosis of the renal artery should be considered eligible for study participation if the P1 at the center feels the disease is not clinically significant.

6. History of drug abuse in the past two years, including narcotics, cocaine, or alcohol (>21 drinks per week).

7. Serious systemic disease that might influence survival or the course of renal disease. (Chronic oral steroid therapy is an exclusion criterion, but steroid-containing nasal sprays are not. Inactive sarcoidosis is not an exclusion criterion.)

8. Clinical evidence of lead intoxication.

9. Arm circumference > 52 cm, which precludes measuring blood pressure with the "thigh" blood pressure cuff. Arm length such that if the cuff that is appropriate for the arm circumference extends into the antecubital space so that the cuff would interfere with placement of the stethoscope over the brachial artery for blood pressure measurement.

10. Clinical evidence of congestive heart failure, current or within the preceding six months; ejection fraction below 35% measured by any method; heart block greater than first degree or any other arrhythmia that would contraindicate the use of any of the randomized drugs.

11. Reactive airway disease, current or in the preceding six months requiring prescribed treatment for more than two weeks.

12. Impairment or difficulty in voiding, precluding adequate urine collections.

13. Intake of nonsteroidal anti-inflammatory agents (NSAIDs) for more than 15 days/month, excluding aspirin. Inability to discontinue NSAIDs or aspirin for five days before GFR measurement.

14. History of severe adverse reaction to any of the randomized drugs required for use in the protocol or contraindication of their use.

15. Pregnancy or likelihood of becoming pregnant during the study period; lactation.

16. Serum potassium level > 5.5 mEq/L at the SV2 and confirmed at G1 for those <u>not</u> on ACE inhibitors during Baseline, or serum potassium level >5.9 mEq/L at the SV2 and confirmed at G1 for those on ACE inhibitors during Baseline.

17. Leukopenia $< 2{,}500/mm^3$ at SV2 and confirmed at the end of Baseline.

18. Medically-indicated need for any of the randomized drugs for any other reason (including angina pectoris, migraine, arrhythmia).

19. Allergy to iodine.

20. Suspicion that the participant will not be able to adhere to medications or comply with the protocol visit schedule.

21. Participation in another intervention study.

The majority of AASK participants were not private patients of AASK investigators. Participants were identified through chart reviews, lab data reviews, or referrals from outside physicians. Participants were located through a variety of methods, including public appeals through the media and mass mailing of brochures. Recruitment techniques have been described (27). The study protocol and consent were approved by each clinical center's Investigational Review Board, and each patient signed an informed consent to enter the study.

Patients identified were first screened informally during conversations with AASK staff and then attended a formal screening, known as the SV-2 visit, at which eligibility criteria were systematically checked. After this, a baseline period was held to confirm eligibility. The baseline period included

- Blood pressure medication back-titration visits, which continued until a patient's diastolic blood pressure was greater than 95 mmHg
- Baseline laboratory and quality of life measures
- Two GFR visits (the first GFR determined study eligibility)

**Randomization**

Data entry at each clinical center was accomplished by remote data entry (over the Internet) into the AASK database, an Oracle database, at the Data Coordinating Center (DCC). When all baseline data were in the database, the clinical center staff members could access the DCC database to request a randomization assignment.

The DCC programs checked that a patient's baseline data were complete, that eligibility requirements had been met, and that a copy of the signature sheet of the patient's consent form had been received. The computer screen then displayed the blood pressure group to which the patient had been randomized (usual or low) and the location of a pair of centrally supplied blinded pill bottles (one with tablets and one with capsules) containing the patient's blinded medication and placebo.

Locations for low, medium, and high doses of medication were provided so that any dosage could be selected and dosage could be switched at any time. The time from SV2 to randomization ranged from two weeks to six months. Randomization schedules were stratified by clinical center. Random permuted blocks with randomly varying block sizes were utilized.

**Follow-Up Visit Schedule**

Soon after randomization, each participant received randomized, blinded drugs (visit FV-0). Participants were then seen at a minimum of once a month for the first six months and

then at a minimum of every two months thereafter. Additional interim visits are held as necessary for blood pressure control.

At each visit, AASK-certified personnel measured seated blood pressure three times and standing blood pressure once with a random zero (RZ) sphygmomanometer. Pill counts of all antihypertensive medications are done at every protocol visit. GFR is measured at 3, 6, and 12 months and every six months thereafter.

Central serum measurements of sodium, potassium, chloride, bicarbonate, urea nitrogen, glucose, creatinine, total protein, albumin, aspartate transaminase, lactate dehydrogenase, alkaline phosphates, total bilirubin, calcium, phosphorus, uric acid, magnesium, gamma glutamyltransferase, total cholesterol, HDL cholesterol, triglycerides, and LDL cholesterol were done every six months.

Central 24-hour urine measurements of urine protein, sodium, potassium, creatinine, and urea nitrogen were also done every six months. Fasting lipid profiles and quality of life measurements (SF 36) were done annually. Throughout follow-up, all medications each patient is taking are logged into the database.

## Clinical Centers and Central Facilities

Each clinical center is staffed with a physician principal investigator (PI), one or more physician co-investigators, a study coordinator, a data entry person, a recruitment/adherence coordinator, a blood pressure interventionist, and a GFR technician. The amount of staffing varied and depended on recruitment goals. One staff member often filled several roles. Each center had a customized recruitment goal, which depended primarily on the population of African Americans from which it could recruit.

Central facilities include the DCC at the Department of Biostatistics and Epidemiology at the Cleveland Clinic Foundation, the Drug Distribution Center, the Central Biochemistry Laboratory, and the Central GFR Laboratory. The DCC coordinated training, documentation, database management, and development of statistical plans, statistical analyses, quality control, reports, and publications. The Drug Distribution Center from the Department of Hospital Pharmacy at the Cleveland Clinic supervises a drug encapsulator (Clinical Encapsulating Services) and a drug packager (McKesson Bioservices). The Drug Distribution Center also coordinated after-hours emergency unblinding through the Cleveland Clinic's Hospital Pharmacy.

Twenty-four-hour urine aliquots and serum samples are sent to the AASK Central Biochemistry Laboratory in the Department of Laboratory Medicine at the Cleveland Clinic for analysis and for storage of afterthought specimens. (Annual urinalysis and CBC whole blood measures are done at each center's local laboratory.) AASK serum and urine specimens for measurement of renal function are shipped to an AASK Central GFR Lab in the Department of Hypertension and Nephrology at the Cleveland Clinic.

## Quality Control

Quality control requirements for the AASK are specified in the study protocol and carried out under the leadership of the AASK Quality Control Committee and the DCC. All staff members were trained and certified at the start of the study. Special Quality Control systems were established for monitoring blood pressure measurement, drug distribution, biochemistry, GFR, and data quality control, and site visits were performed.

### Blood Pressure Quality Control

AASK seated blood pressure measurements are taken after measurement for proper cuff size. A patient rests quietly for five minutes, pulse is taken, and steps for determining the random zero sphygmomanometer's peak inflation level and zero value are followed. Protocol procedures are followed as seated blood pressure is measured three times. The average of the last two measures is considered the AASK blood pressure level.

Each of the 21 AASK Clinical Centers has a centrally-trained blood pressure trainer, who is responsible for the overall blood pressure measurement quality at that center. The 21 trainers are recertified annually by a blood pressure consultant. The trainers are responsible for training and supervising the person who will measure blood pressure at their centers. Quarterly quality control readings are done with each blood pressure measurer working side by side with the blood pressure trainer. The DCC provides the Quality Control Committee with various measures of blood pressure quality, including intra-test coefficients of variation and digit preference in the blood pressure measurements and in the sphygmomanometer's zero values.

### Drug Distribution Quality Control

At every visit at which blinded drugs are dispensed, clinical centers enter into the database random drug code numbers assigned by the DCC that are on the bottles given to the patient. Database programs determine whether the correct bottles were dispensed.

### Biochemistry Quality Control

For quality control of the Central Biochemistry Lab's serum and urine measurements, the clinical centers send split samples to the central lab twice annually. The lab measures the second sample blinded, and the DCC compares the two measurements for the Quality Control Committee.

### GFR Quality Control

Central training and certification is required for each person who will be measuring GFR on AASK patients. A GFR consists of four "periods" of time, each of which begins with a serum collection and ends with a urine collection. An estimated GFR is calculated for each of the four periods; the AASK GFR is a weighted average of the GFR's of the individual periods. The DCC monitors various aspects of GFR quality, including the

coefficient of variation of the four estimated GFR's. Each clinical center's rate of missed GFR measurements is monitored by the Quality Control and Adherence Committees.

For quality control of the Central GFR Lab, the clinical centers send split samples to the central GFR lab twice annually. The GFR lab measures the second sample blinded to whose specimen it is, and the DCC compares the results of the two GFR's.

### Data Quality Control

Data are entered at the clinical centers and are double entered, or rekey verified, at the clinical centers. Edit checks are applied at the time of data entry and during data analysis. The DCC and Quality Control Committee monitor time to data entry, time to response to data discrepancy inquiries, and the time it takes the DCC to correct data.

### Site Visits

Each clinical center had at least two site visits: One in the first two years of the study focusing on recruitment issues and a second later in the study focusing on quality control. The two-day quality control site visits consisted of a brief data audit and a detailed discussion of patient adherence, patient retention, protocol adherence as to choice of antihypertensive agent, and the clinical center's protocol adherence, achieved separation between blood pressure groups, and quality control.

## Objectives of the AASK

### Primary Outcome and Objectives

The primary objective of the AASK is to determine if the low blood pressure goal (compared to the usual blood pressure goal) or the use of a specific antihypertensive regimen reduces the mean rate of change in GFR during follow-up. The primary analysis will compare the rate of change in GFR between the following treatment groups:

- Low vs. usual blood pressure goals
- ACEI vs. BB regimens
- DHPCCB vs. BB regimens

Assuming comparable blood pressure levels can be achieved within the antihypertensive agent arms, the comparisons (ACEI) and (DHPCCB) will treat the BB arm as a control group to determine if the ACEI or DHPCCB regimens have renoprotective effects independent of blood pressure level. The ACEI and DHPCCB groups will also be directly compared in secondary analyses. However, as described below, this comparison is expected to be complicated by opposite hemodynamic effects projected from the ACEI and DHPCCB interventions. The study's primary renal analysis considers GFR slopes;

the study's main patient-outcome analysis considers rates of renal events, which includes reduction in GFR by 50%, reaching end stage renal disease, or death.

**Assessment of Renal Function for GFR Slope**

Assessment of the effects of the AASK interventions is complicated by the expectation that the interventions will have differing hemodynamic effects on GFR during the first three months that the patient is on the intervention. These hemodynamic effects are distinct from each intervention's hypothesized long-term effects of the agents on the progression of kidney disease. Past studies have suggested that initially, ACEIs may reduce GFR by 2% to 6% (32-34), DHPCCBs may increase GFR by 2 % to 4% (35-36), BBs may reduce GFR by 1% to 2% (35,37), and the low blood pressure goal may reduce GFR by 2% (38). Some research suggests that the initial hemodynamic effects persist as long as the patients remain on their respective interventions and that, at least for ACEIs, the effect is reversible on termination of the therapy (39, 40).

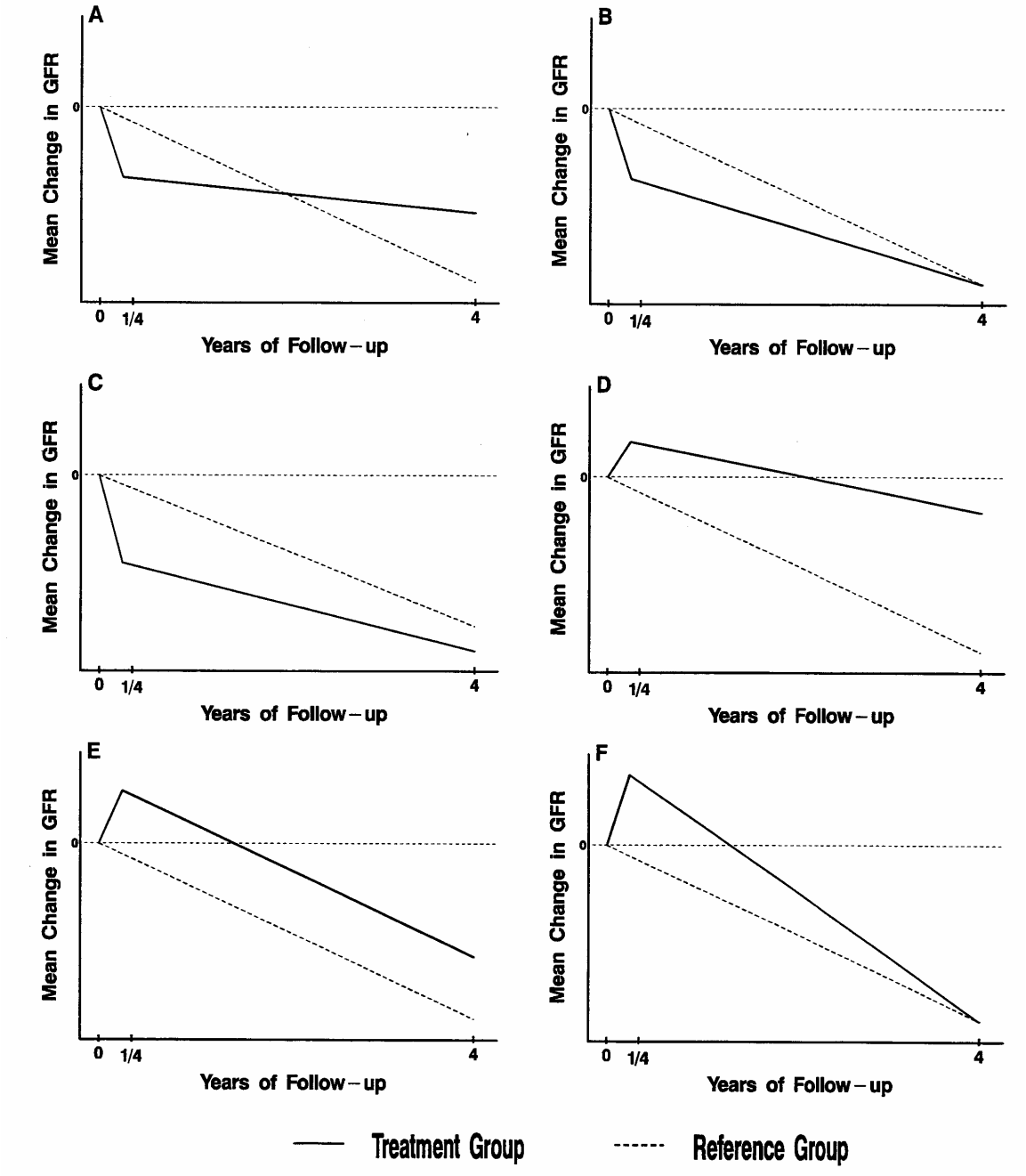
Several possible scenarios for the comparison of mean changes in GFR between treatment and reference groups are presented in Figure 1.

**Figure 1. Possible Scenarios for the Comparison of Two Treatment Groups**

Shown below are six alternative scenarios for the effects of a treatment compared to a reference group on the mean change in GFR from baseline to four years under the 2-slope model. The chronic slope is depicted by the slope from three months (1/4 year) to four years, and the total mean slope as the average rate of change from baseline to four years.

Panels A and D represent definitive scenarios in which the comparisons between treatment groups of the mean chronic and total slopes are in agreement. The remaining panels depict inconclusive scenarios in which the comparisons of the chronic and total means slopes are not in agreement.

# Figure 1


A
B
C
D
E
F
Mean Change in GFR
0
0
1/4
4
Years of Follow-up
Treatment Group
Reference Group

Scenario A represents expected comparisons of the blood pressure goals (or the ACEI vs. BB regimens) under the research hypothesis of long-term beneficial effects of the lower goal (or the ACEI regimen), following the expected initial hemodynamic effects. Scenarios B and C are also consistent with the research hypothesis of beneficial effects of these interventions. In Scenarios B and C, the planned AASK follow-up of three to six years is not sufficient for the hypothesized long-term beneficial effects to overcome the regimens' initial hemodynamic effects. Scenarios D through F represent potential results for the DHPCCB vs. BB comparison based on the expected initial increase in GFR in the DHPCCB group.

To clarify these scenarios, we divide the follow-up period into two phases. The acute phase consists of the first three months after randomization, during which hemodynamic effects are expected to occur. The chronic phase consists of the remainder of follow-up after three months. Two separate primary hypotheses are stipulated for each of the three primary treatment group comparisons:

- $HO_1$: There will be no difference between treatment groups in the mean rate of decline in GFR during the chronic phase.

- $HO_2$: There will be no difference between the treatment groups in the mean total rate of decline in GFR from baseline to the end of follow-up (taken to be four years).

The hypothesis $HO_1$ may be criticized since it pertains to a change in the outcome variable starting three months after randomization, when a patient's renal function has already been modified by the randomized treatment. However, if the hemodynamic effects persist while the patients remain on the respective treatments, the rate of change in GFR during the chronic phase should reflect the actual rate of disease progression independently of the hemodynamic effect.

By contrast, assessment of $HO_2$ is influenced by the initial hemodynamic effect in addition to the long-term effects during the chronic phase, and is thus dependent on the duration of the study; it may not accurately reflect the long-term course of the disease. Nonetheless, if the total mean rate of decline in GFR from baseline to the end of the study is not different between two treatment interventions, it is not clear that a difference in the rate of change of GFR during the chronic phase alone would provide convincing evidence that an intervention will continue to slow a patient's disease progression after the end of the study and ultimately delay the onset of ESRD.

Therefore, the AASK will be regarded as conclusively establishing a benefit of one intervention over another only if $HO_1$ and $HO_2$ are both rejected in the same direction. Thus, Panels A and D of Figure 1 represent unambiguous cases where the treatment would be declared beneficial; the remainder represent ambiguous scenarios where only one of $HO_1$ or $HO_2$ are false, or where both $HO_1$ and $HO_2$ are false, but in opposite directions.

## Primary Analysis

The primary analysis of GFR will be carried out using a 2-slope mixed-effects model (4 1, 42) with different slopes in the acute and chronic phases. The fixed-effects component models the effects of the treatment groups on the mean GFR slopes during the two phases, while the random-effects component includes random intercepts, acute and chronic slopes for each patient, plus random deviations of the individual GFR measurements. Linear splines are used so that the regression lines in the acute and chronic phases join at three months for both the fixed and random effects. Contrasts between mean slopes in the respective treatment groups will be used to test the effects of the treatments on the acute and chronic slopes, and on the total mean slope from baseline to four years (48 months). The total mean GFR slope will be estimated for each treatment group as the weighted average (3/48) $\beta_{acute}$ + (45/48) $\beta_{chronic}$, where $\beta_{acute}$ and $\beta_{chronic}$ denote the mean slopes per month during the acute and chronic phases, respectively.

The comparisons of the chronic slopes and the total mean GFR slope to four years will be used to test the primary hypotheses $HO_1$ and $HO_2$. If the comparison of two treatment groups is significant in the same direction for both the chronic and total mean slopes, then we will conclude that the treatment group with the less steep slopes is likely to ultimately delay the onset of ESRD. In order to increase the precision of the estimated treatment effects, the following variables, which are expected to be associated with the GFR slopes, will be included as covariates: age, gender, history of cardiovascular disease, baseline MAP, baseline urine protein excretion, and clinical center. In accordance with the factorial design, both main effects and interactions between the blood pressure level and anti-hypertensive agent factors will be tested. However, qualitative interactions between the treatment interventions are not expected, and it is recognized that the power to detect an interaction and for comparing individual cells should an interaction be detected will be limited. The primary analysis will be intent-to-treat, so that patients reaching stop points requiring modifications of their study treatments will continue to be followed and retained in their original randomized groups for analysis.

## Multiple Hypothesis Tests and Interim Stopping

Six annual interim analyses are planned, including the final analysis. Lan-DeMets spending functions (43) will be used to maintain the total type I error rates at 5% separately for the comparisons of chronic and total mean slopes for each of the three primary treatment group comparisons. O'Brien-Fleming (44) stopping boundaries will be used, with two-sided tests for each comparison. The information fractions are obtained separately for the chronic and total mean GFR slopes by computing the ratio of the expected variance of the test statistic at the final analysis to the variance at the current interim analysis. The stopping rule stipulates that a treatment group comparison may be terminated if the stopping boundary is crossed in the same direction for both the chronic and total mean slopes. Secondary analyses will also be considered in deciding whether to terminate an intervention, if an intervention is terminated, we expect to reassign the patients on the discontinued intervention and to continue investigating the remaining interventions.

Conditional power will be evaluated at each interim analysis. Consideration will be given to terminating the study early if the conditional probability of obtaining a conclusive result (e.g., obtaining significance for the comparisons of both the chronic slopes and the total change in GFR) is found to be low for each of the three primary treatment group comparisons.

Hypothesis tests are carried out separately for $HO_1$ and $HO_2$ using comparison-wise, two-sided significance levels of 5% for each of the three primary treatment group comparisons. We decided against using a multiple comparisons procedure for the ACEI vs. BB and DHPCCB vs. BB comparisons because the potential renoprotective effects of ACEIs and DHPCCBs have different biological mechanisms. Thus, these comparisons evaluate distinct hypotheses. Our requirement that the comparisons of chronic and total mean slopes be separately tested at the 5% significance level is conservative, because the probability that the comparisons of chronic and total mean slopes would both reach significance at the 5% level under the joint null hypothesis $HO_1 \cap HO_2$ is less than 0.05. We decided against relaxing the rejection criteria to obtain a joint significance level of 5% because it was felt that both the comparisons of chronic slopes and the total change in GFR must be significant at the 5% level to be convincing to the nephrology community.

**Time-To-Event Analyses**

The potential ambiguities of the analysis of GFR slopes illustrated in Figure 1 suggest that it might be advisable to consider alternative outcomes based on hard clinical endpoints. For studies of chronic renal disease, a logical choice is ESRD, which occurs when GFR declines to 7 to 10 ml/minll.73m$^2$, at which point a renal transplant or artificial dialysis is required to support life. However, the expected rate of ESRD in the AASK is too low to for this outcome alone to provide sufficient power. As an alternative, a time-to-event analysis will be conducted based on the following composite:

- Reduction of GFR by 50% or by 25 ml/min/1 .73m$^2$ from the mean of the two baseline GFRs, confirmed by a repeat GFR
- ESRD
- Death

Time-to-event analyses based on the time to a pre-specified change in a marker of renal function have been used as the primary analysis in previous clinical trials (30, 31). Events such as dialysis and death are considered to be “harder” endpoints than GFR slope and thus, potentially more relevant to the patients involved. The time-to-event analysis will be carried out using Cox-regression (45) with age, gender, history of cardiovascular disease, baseline MAP, and baseline urine protein excretion included as covariates.

**Assessments of 2-Slope Mixed Effects Model**

The assumptions of the 2-slope mixed effects model will be examined (42). Potential deviations include nonlinearity of the mean GFR decline during the chronic phase and misspecification of the random component of the model. The linearity of the decline in mean GFR will be assessed by fitting multi-slope spline models with changes in slope allowed at each protocol GFR measurement. Possible misspecifications in the random component will be assessed by comparing the variance components of the random effects between the treatment groups and other patient subgroups, evaluating alternative error structures for the random effects, and by comparing the model-based standard errors to robust sandwich-type standard errors. If major deviations from the 2-slope model are detected, consideration will be given to generalizing the 2-slope model to incorporate them.

**Informative Censoring**

Patients may become lost to further GFR follow-up in the AASK due to any of the following:

- Reaching ESRD, which precludes further GFR measurements
- Death
- Otherwise dropping out and becoming lost to GFR follow-up

Informative censoring will occur if the dropout times are correlated with the GFR slopes conditionally on the treatment factors, baseline covariates, and observed GFRs. If the distribution of dropout times differs between the randomized groups, informative censoring may lead to biased estimates of the treatment effects under the mixed effects model. The risk of informative censoring will be evaluated during the study by carrying out statistical simulations of the potential bias resulting from the observed distributions of dropout times in the respective treatment groups. If the possibility of a substantial bias is detected, we will consider implementing a random-coefficient selection model (46) or a random-coefficient pattern mixture model (47) in order to adjust for the censoring process in the analysis.

**Other Key Secondary Analyses**

If the follow-up MAP level exhibits any difference between the anti-hypertensive agent arms, we will repeat the analyses comparing the anti-hypertensive agent groups after adding follow-up MAP as a covariate in order to assess the renal protective effects of the antihypertensive regimens independently of the level of blood pressure. The change in proteinuria from baseline and the rate of cardiovascular hospitalization and death are secondary outcomes. All cardiovascular events, including cardiovascular deaths and hospitalizations for myocardial infarctions, strokes, heart failure, revascularization procedures, and other hospitalized cardiovascular events were reviewed and classified by a blinded endpoints committee according to a pre-specified protocol.

## Statistical Power

Statistical power was evaluated by statistical simulation for a variety of scenarios based on published results on African Americans from the HDFP trial (15) and a study of African Americans with hypertensive nephrosclerosis completed shortly before the AASK trial (23), as well as patient data from the AASK Pilot (26) and the MDRD Study (22,24), which was available to the DCC. Table 3 presents the estimated power based on a representative set of assumptions, including:

- A three-year uniform recruitment period with three years of further follow-up, yielding a total sample size of 1,094
- The initial decline in mean GFR from baseline to three months is 2 ml/min/l.73m$^2$ greater for the lower than the usual blood pressure group, 2 ml/min/1.73m$^2$ greater for the ACEI than the BB group, and 2 ml/min/1.73m$^2$ less for the DHPCCB than the BB group
- The between-patient standard deviation of GFR slopes is 3.8 ml/min/1.73m$^2$/yr, the within-patient variance of GFRs is equal to 0.67 of the patients current GFR value
- The rate of loss to GFR follow-up is 4% per year
- The rate of "cross-overs" between treatment arms is 4% per year
- The mean chronic slope in the control groups for the respective comparisons (e.g., the BB group for the two antihypertensive agent comparisons, and the usual goal for the blood pressure comparison) is between -2 and -4 ml/min/1.73m$^2$/yr
- The death rate in the control groups is 10% per five years

The table presents the power of the study to detect a 30% proportional reduction in GFR slope in the treatment group for each of the three main comparisons, with no effect assumed for patients with slopes greater than or equal to 0. For purposes of comparison, power is provided for acute effects of 0 in addition to the acute effects projected in assumption 2. A sided significance level of 5% is used for each analysis. For the time-to-event analysis, the mortality rate is also hypothesized to be 20% lower in the treatment than in the control groups.

Assuming a mean GFR slope of -4 ml/min/1.73m$^2$/yr, the power for the primary treatment group comparisons ranges from 88% to 99% for the analysis of chronic slopes, and from 62% to 99% for the analysis of the total mean GFR slope. Due to the assumption that the size of the treatment effect will be proportional to the GFR slope in the control group, the power of both the analysis of chronic slopes and especially the total GFR slopes is reduced substantially if less steep mean slopes are assumed (48). The

power for the secondary time-to-event analysis is also lower for the slower than for the faster assumed mean progression rates, but the dependence of the power of the time-to-event analysis on the mean slope is less than for the analysis of GFR slopes. The power of the analysis of total mean GFR slope is greater for the DHPCCB vs. BB comparison than the ACEI vs. BB or the lower vs. usual blood pressure goal comparisons due to the expectation of a positive initial hemodynamic effect of DHPCCB on GFR, but a negative initial hemodynamic effect for the other interventions. It is for this reason that a smaller sample size was used in the DHPCCB group than for the ACEI and BB groups.

## Discussion

African Americans have a higher prevalence of hypertension than Whites, and if hypertension is present, are more likely to develop renal insufficiency (49). Once renal insufficiency is present, African Americans with hypertension have a more rapid rate of decline in renal function than Whites (15, 50, 51). Thus, identifying interventions that slow the decline in renal function in African Americans with hypertensive nephrosclerosis represents an important healthcare priority.

Although nonrandomized studies have suggested that lower blood pressure preserves renal function in persons with hypertension (52), the absence of randomization to a specific blood pressure goal makes the data difficult to interpret. The patients with lower or higher achieved blood pressures may have other variables present that account for observed outcomes (e.g., milder hypertension or other determinants of renal disease progression). In the AASK, participants were randomly assigned to one of two blood pressure goals, thus reducing confounding factors. The biopsies performed in the pilot trial verified that the study's entry criteria selected patients who actually had hypertensive nephrosclerosis (26), a feature not present in previous studies.

The MDRD Study reported a beneficial effect of random assignment to a low blood pressure goal in patients with renal disease associated with proteinuria, although not in its intent-to-treat analysis including all randomized patients (22, 53). The reported benefit of the low goal in MDRD patients with proteinuria provides a precedent for a benefit of a lower blood pressure goal in a particular subpopulation with chronic renal disease. However, the MDRD had few African Americans, and hypertensive nephrosclerosis is usually not associated with a high degree of proteinuria. The randomized comparison of the blood pressure goals in the AASK will test whether reducing blood pressure to levels below those recommended for the general hypertensive population slows progression of renal disease in African Americans with hypertensive nephrosclerosis, and will also address the alternative hypothesis that there is a blood pressure below which there will be a negative effect on renal outcomes (54).

Previous randomized trials have demonstrated that ACEIs slow the progression of renal disease in patients with diabetic nephropathy and chronic renal insufficiency associated with proteinuria (30 31, 55). DHPCCBs are widely used antihypertensives in African Americans, and are also hypothesized to have renoprotective effects. The AASK will test

whether ACEIs and DHPCCBs are renoprotective in African Americans with hypertensive nephrosclerosis by comparison with a reference group assigned to first-line therapy with a BB and the same target blood pressure level. The use of a BB as the reference for testing the renoprotective effects of ACEIs could be criticized because BBs and ACEIs share certain properties in that they both inhibit renin release, but the inhibition of the renin angiotensin system by BBs is far less than inhibition by ACEIs.

Data from the AASK pilot study and other studies suggest that the interpretation of the analysis of GFR slope could be complicated by an acute (first three months) increase in GFR in the DHPCCB group and acute declines in GFR in the ACEI group and in the low blood pressure group. These acute modifications of GFR are generally thought to be hemodynamic effects without clinical significance, and for ACEIs have been shown to be reversible after termination of therapy (38-40). For treatment group comparisons in which the early hemodynamic effect is in the opposite direction of the long-term effect on the decline in renal function, it is possible that effects of the treatment groups in the acute and chronic phases of the study could cancel, rendering the analysis of mean GFR slope inconclusive (see Figure 1).

In contrast to the analysis of GFR slope, which addresses the mean drug effect on renal function in all patients, including those with little or no GFR decline, the secondary outcome of time to a GFR event (halving of GFR), ESRD, or death is based on events of clear clinical impact, either large declines in renal function or death. Because the magnitude of the hypothesized acute effects on GFR were much smaller than the changes in GFR required to trigger a GFR event or ESRD, the composite outcome is expected to be less sensitive to the acute effects than the mean GFR slope (56). This point is illustrated by Table 3, which indicates that the power of the time-to-event analysis is greater than that of the total GFR slope when the acute effects are in the opposite direction of the hypothesized long-term effect, particularly when the magnitude of the mean slope in the reference group is small.

The AASK study is the first clinical trial to address a critical healthcare issue, the progressive loss of renal function in African Americans with hypertensive nephrosclerosis and to demonstrate whether or not specific MAP goals or specific antihypertensive agents better preserve renal function.

| Table 3. Power of Main AASK Comparisons[1] | | | | | |
|---|---|---|---|---|---|
| **Treatment Group Comparison** | **Assumed Acute Effect (ml/min/1.73m$^2$ per 3 mos.)** | **Assumed Mean Slope in reference Group (ml/min/1.73m$^2$ per year)** | **Chronic Slope** | **Analysis Method—Total Mean Slope from Baseline to 4 yrs.** | **Time-to-Event** |
| **Low vs. Usual Blood Pressure Goal** | -2 | -4<br>-3<br>-2 | 99<br>95<br>78 | 71<br>42<br>14 | 87<br>78<br>65 |
| | 0 | -4<br>-3<br>-2 | 99<br>95<br>78 | 99<br>98<br>86 | 99<br>97<br>91 |
| **ACEI vs. BB** | -2 | -4<br>-3<br>-2 | 97<br>90<br>69 | 62<br>35<br>12 | 79<br>68<br>55 |
| | 0 | -4<br>-3<br>-2 | 97<br>90<br>68 | 99<br>95<br>77 | 98<br>93<br>84 |
| **DHPCCB vs. BB** | +2 | -4<br>-3<br>-2 | 88<br>76<br>51 | 99<br>99<br>95 | 98<br>95<br>84 |
| | 0 | -4<br>-3<br>-2 | 88<br>76<br>51 | 92<br>83<br>60 | 91<br>81<br>68 |

[1]See text for other assumptions of power analysis.

[2]Assumed acute effects represent difference between projected mean change in GFR between baseline and 3 months in the treatment group and the reference group for each comparison.

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# Appendix D. Design of the AASK Cohort Study

## The Rationale and Design of the AASK Cohort Study

(In Press, *JASN*)

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## Abstract

Hypertensive kidney disease commonly progresses. The primary objective of the African American Study of Kidney Disease and Hypertension (AASK) Cohort Study is to determine prospectively the course of kidney function and risk factors for kidney disease progression in African-Americans with hypertensive kidney disease who receive recommended antihypertensive therapy.

The AASK Cohort Study is a prospective, observational study that is an extension of the AASK trial. The AASK trial tested the effects of three medications (ramipril, metoprolol, and amlodipine) used as initial antihypertensive therapy and two levels of blood pressure control. Of the 1,094 trial participants, approximately 650 to 700 individuals who have not reached end stage renal disease (ESRD) will likely enroll in the Cohort Study. Risk factors to be studied include environmental, genetic, physiologic, and socio-economic variables. The primary renal outcome is a composite clinical outcome defined by doubling of serum creatinine, ESRD, or death. Medication treatment for hypertension, beginning with the angiotensin converting enzyme inhibitor, ramipril, is offered to all participants. In this fashion, the study directly controls two of the major determinants of kidney disease progression (treatment of hypertension and use of renoprotective, antihypertensive medication). The minimum duration of follow-up in the Cohort Study is 5 years (total of 9 to 12 years, including the period of the AASK trial).

Ultimately, data from the AASK Cohort Study should enhance our understanding of the risk factors and processes that determine the progression of kidney disease. Such results might eventually lead to new strategies that delay or prevent ESRD.

## Introduction

During the past three decades, mortality from cardiovascular and cerebrovascular disease has progressively declined. In contrast, no such reduction in the mortality has occurred in end-stage renal disease (ESRD). In fact, the number of patients entering the ESRD program in the United States has doubled during the past decade (1989-1998). Consequently, the number of persons with ESRD in the United States exceeds 300,000, and the annual cost to the Medicare ESRD Program is over $15 billion.'

ESRD disproportionately affects African-Americans. Although African-Americans comprise only 13% of the general U.S. population, 29% of incident ESRD cases in 1999 occurred in African-Americans.[1] After adjustment for age and gender, the incidence of all-cause ESRD is nearly four times greater in African-Americans than in whites (953 vs. 237 cases per million in 1999). The corresponding incidence of hypertensive ESRD is over six times greater in African-Americans than whites (3,187 vs. 515 incident cases per 10 million). Two strategies that might prevent hypertensive ESRD are

- Use of antihypertensive medications that have renoprotective effects apart from their effects on blood pressure (BP)

- Aggressive BP control, that is, a BP goal that is below current recommendations

The African American Study of Kidney Disease and Hypertension (AASK) was a 2 x 3 factorial trial that tested these two strategies. Participants were 1,094 African-Americans, ages 18-70 years, who were hypertensive with a glomerular filtration rate (GFR) of 20 to 65 ml/min/1.73m$^2$, and no other apparent cause of renal insufficiency other than hypertension. Participants were randomized to a usual mean arterial pressure (MAP) goal of 102-107 mmHg or a low MAP goal of < 92 mmHg, and to initial treatment with one of three antihypertensive study drugs: a sustained-release B-blocker (BB), metoprolol; an angiotensin converting enzyme inhibitor (ACEI), ramipril; or a dihydropyridine calcium channel blocker (DHPCCB), amlodipine. The primary outcome was GFR slope, as assessed by $^{125}$I-iothalamate clearance. A secondary renal outcome was a composite clinical outcome defined by the occurrence of a reduction in GFR by 50% or by 25-ml/min/1.73m$^2$ from baseline, ESRD, or death.

Trial results have been published.[2, 3] In brief, the presence of even small amounts of proteinuria at baseline (urinary protein to creatinine ratio [UP/Cr] of > 0.22) was associated with rapid progression of kidney disease. Despite a sustained 10 mmHg MAP difference between the two MAP groups, progression of kidney disease was similar in both groups. Ramipril as compared to metoprolol appeared to slow renal disease progression independent of protein level, while ramipril and metoprolol slowed progression as compared to amlodipine in patients with baseline UP/Cr >0.22.

These results have implications for the Cohort Study. First, the incidence of clinical outcomes and the progression of kidney disease were high, even in the group that received the most effective therapy. Specifically, in the ramipril group, the cumulative incidence of clinical outcomes was ~30% over five years, and the average annual decline in GFR was 1.9 ml/min/1.73m$^2$/yr. This documented decline in renal function, which is roughly twice the average age-associated decline in GFR in the general population, highlights the importance of identifying factors other than BP that predict, if not determine, progression of hypertensive kidney disease. Second, of the three medications tested in AASK, ramipril had the most beneficial effects on kidney function. These results support provision of ramipril therapy to all participants in the AASK Cohort Study.

In view of these results, the primary objective of the AASK Cohort Study is to determine prospectively the long-term course of kidney function and risk factors for kidney disease progression in African-Americans with hypertensive kidney disease. We hypothesize that in addition to BP control and the use of recommended renoprotective, antihypertensive medication, other factors determine the progression of kidney disease. A secondary objective is to determine the occurrence of cardiovascular disease and assess its risk

factors. In this context, the AASK Cohort Study addresses the following research questions:

- What is the long-term course of kidney function in this population?
- What are the environmental, genetic, physiologic, and socio-economic factors that predict the progression of kidney disease?
- What are the long-term effects of the AASK trial interventions on the progression of kidney disease?
- Does the development of proteinuria predict the progression of kidney disease?
- What is the impact of recommended BP therapy, as determined by the AASK trial, on the progression of kidney disease in comparison to usual care in the community? This question will be addressed using parallel analyses from the Chronic Renal Insufficiency Cohort (CRIC) study.
- What comorbidities, particularly cardiovascular disease, occur in the setting of hypertension-related kidney disease?
- What risk factors predict the occurrence of cardiovascular disease?
- What are the patterns of change in metabolic variables and cardiovascular-renal risk factors during the transition from pre-ESRD to ESRD?

## Methods

The AASK Cohort Study is a multi-center, prospective, observational study that is an extension of the AASK trial (see figure). Institutional review boards at each center approved the study protocol. A data and safety monitoring board provides external oversight.

### Study Population

The study population of the AASK Cohort Study consists of all randomized persons in the AASK trial who did not reach ESRD by the end of the trial. Those who reached ESRD during the trial are invited for one visit at which DNA is collected; otherwise, no additional data are collected.

### Data Collection

The purpose of the study visits is to collect risk factors (exposure) data, ascertain outcomes, and manage antihypertensive therapy. Data collection for exposures and outcomes are collected at baseline and every 12 months thereafter. Management of

antihypertensive therapy occurs at these visits and at an additional two to four visits/year. While participants are encouraged to receive their antihypertensive care through the AASK Cohort Study, some persons may decide not to accept such care. In this case, they are asked to attend just the semi-annual data collection visits. Clinical outcomes are ascertained at each contact.

Table 1 displays the data collection items and procedures by visit during the first two years. The pattern of data collection items and visits during all subsequent years is similar to that of year 2, except that ambulatory BP monitoring and echocardiography occur every other year. For those persons who reach ESRD during the Cohort Study, data collection visits still occur. Core measurements are as follows:

- Blood pressure. BP is measured in a standardized fashion by trained, certified observers using the Tycos Classic Handheld Aneroid device. Two BP measurements are obtained in the seated position and one measurement in the upright position.

- Biological Specimens. Blood is obtained twice at baseline and then every six months thereafter. Serum creatinine is measured at each point. On an annual basis, fasting lipids [total cholesterol, LDL cholesterol (calculated), HDL cholesterol and triglycerides], glucose, insulin, routine chemistry panel, and CBC are measured. Other analytes include homocysteine, C-reactive protein (CRP), and potentially other measures of inflammation, measures of oxidative stress, and other lipid risk factors, e.g., Lp(a). DNA is collected once. From this specimen, DNA is isolated and stored, and lymphocytes immortalized. DNA is also dried and archived. From each collection, aliquots of serum and plasma are banked for future analyses.

- 24-hour urine. A 24-hour urine collection is obtained annually. Analytes include creatinine, protein, albumin, sodium, and potassium. From each collection, aliquots are banked.

- Fingernail clippings. Finger nail clippings are collected once each year. Participants are asked to trim each of their 10 fingernails with a chromium-free nail clipper. From these stored clippings, the levels of 50 heavy metals, including elemental mercury, chromium, and lead, can be measured using neutron activation analyses.

- Questionnaires. are administered annually that focus on potential risk factors. Surveillance for outcomes (ESRD and cardiovascular outcomes) occurs at each visit. Risk factors of interest include health habits (alcohol, smoking, analgesic use, drug use), medications, exposure to IV contrast, and psycho-social factors. Instruments include the SF36, the Jackson Heart Study Approach to Life, the Beck Depression Inventory II, and the Diener Satisfaction of Life Form.

- Cardiovascular (CVD) procedures. All CVD procedures are done locally and read centrally by the Cardiovascular Procedures Core Laboratory at Lenox Hill Hospital. Each year, an ECG is obtained. Specific codes of interest are the presence of LVH and myocardial infarction.

- Echocardiogram. At baseline and every other year, a 2-dimensional, M-mode, pulsed Doppler and pulsed tissue Doppler echocardiogram is obtained to evaluate left ventricular (LV) structure, LV mass, cardiac output, and aortic valve structure, and to obtain measures of systolic and diastolic function.

- 24-hour blood pressure recordings. At baseline and every other year, 24-hour ambulatory BP recordings are obtained. The study uses the SpaceLabs™ 90217 Ultralite or SpaceLabs™ 90207 devices. During each 24-hour recording, measurements are obtained every 30 minutes throughout the day and night, from which awake and asleep averages are calculated, along with other variables including dipping status.

| Table 1: AASK Cohort Study Data Collection Items and Activities by Visit during the First Two Years of the AASK Cohort Study | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **C0** | **C0.1** | **C3** | **C6** | **C9** | **C12** | **C15** | **C18** | **C21** | **C24** |
| **Informed Consent** | X | | | | | | | | | |
| **Contact Information** | X | | X | X | X | X | X | X | X | X |
| **BP Measurement** | X | X | X | X | X | X | X | X | X | X |
| **BP Management** | X | X | X | X | X | X | X | X | X | X |
| **Weight** | X | X | X | X | X | X | X | X | X | X |
| **Demographics and Baseline Medical Hx Questionnaire** | X | | | | | | | | | |
| **Medication Questionnaire** | X | X | X | X | X | X | X | X | X | X |
| **Other Risk Factors** | X | | | | | X | | | | X |
| **Surveillance for Outcomes** | | | X | X | X | X | X | X | X | X |
| **Fasting blood for lipids, glucose, insulin, routine chemistry, CBC** | X | | | | | X | | | | X |
| **Creatinine** | X | X | | X | | X | | X | | X |
| **DNA** | X | | | | | | | | | |
| **24-hour urine** | X | | | | | X | | | | X |
| **Finger nail clippings** | X | | | | | X | | | | X |
| **Stored Specimens** | X | | | X | | X | | X | | X |
| **Electro-cardiogram** | X | | | | | X | | | | X |
| **Ambulatory BP** | X | | | | | | | | | X |
| **Echo-cardiogram** | X | | | | | | | | | X |

* Visit code: C followed by a number corresponds to months after enrollment, for example, C18 is the cohort visit which is 18 months after enrollment. Visit C0.1 occurs just after the initial visit

## Outcomes

Major outcomes of interest are renal and cardiovascular events. The primary renal outcome is a composite clinical outcome defined the occurrence of a marked reduction in kidney function, ESRD, or death (G1 or S1, see Table 2). A co-primary outcome includes just the renal events (marked reduction in kidney function or ESRD) without deaths (G2 or S2, see Table 2). Secondary outcomes are GFR slope, to be used in mechanistic analyses, and proteinuria. During the trial, GFR was measured using $^{125}$I-iothalamate clearance. After the end of the trial, estimated GFR (eGFR) is calculated from serum creatinine using an equation developed from baseline data in the AASK trial.[4]

**Table 2: AASK Cohort Study Renal Outcomes by Period**

**COMPOSITE CLINICAL OUTCOMES (PRIMARY OUTCOMES)**

**Period 1 (AASK Trial)**
G1: the occurrence of a 25 ml/min/1.73m$^2$ or 50% reduction in GFR from trial baseline, ESRD (dialysis or transplantation), or death
G2: the occurrence of a 25 ml/min/1.73m$^2$ or 50% reduction in GFR from trial baseline or ESRD (dialysis or transplantation)

**Period 2 (AASK Trial and AASK Cohort)**
S1: Doubling of serum creatinine from trial baseline, ESRD (dialysis or transplantation), or death
S2: Doubling of serum creatinine from trial baseline or ESRD (dialysis or transplantation)

**Period 3 (AASK Cohort)**
S1: Doubling of serum creatinine from cohort baseline, ESRD (dialysis or transplantation) or death
S2: Doubling of serum creatinine from cohort baseline or ESRD (dialysis or transplantation)

**GFR SLOPE (SECONDARY OUTCOME)**

**Period 1 (AASK Trial)**
Mean slope from serial GFR measurements ($^{125}$I-iothalamate clearance)

**Period 2 (AASK Trial and AASK Cohort) and Period 3 (AASK Cohort):**
Mean slope of estimated GFR (eGFR) in which eGFR = 329 x $(Scr)^{-1.096}$ x $(age)^{-0.294}$ x (0.736 for women). This equation was developed from baseline data of the AASK trial (Lewis, 2001).

**PROTEINURIA (SECONDARY OUTCOME)**

**Same outcomes in Period 1, 2, and 3:**
Urine protein/urine creatinine ratio (UP/Cr), a continuous variable
The occurrence of UP/Cr > 0.22 (roughly 300 mg/day of proteinuria)
The occurrence of UP/Cr > 0.66 (roughly 1 gm/day of proteinuria)

The classification of clinical cardiovascular outcomes is displayed in Table 3. 'Total' cardiovascular outcomes include both 'definite' and 'probable' outcomes. In most analyses, cardiovascular outcomes are grouped together as a composite outcome; however, in some instances, cause-specific events are of interest. A Cardiovascular Outcome Committee, blinded to risk factor status, reviews medical records and assigns outcome status.

**Table 3: AASK Cohort Study Clinical Cardiovascular Outcomes**

**"Definite" Cardiovascular Outcomes:**

Cardiovascular death, OR

Cardiac revascularization procedure, OR

Non-fatal myocardial infarction, defined as a clinical report of myocardial infarction from the investigator and the presence of one of the following:

(1) Elevation of CPK > 2 times the upper limit of normal for the given hospital, supported by the elevation of cardiac-specific enzyme above the normal range such as MB fraction or cardiac troponin, OR

(2) in the absence of cardiac specific enzymes, determination of a typical evolutionary pattern defined as an elevation of CPK to 2 times the upper limit of normal for the given hospital, followed by a fall of at least 50% or the appearance of new pathological Q-waves in two or more contiguous leads, OR

(3) the appearance of a R-wave with R/S ratio in lead V1 > 1.0 in the absence of another explanation or a loss of progression of R-waves V2 through V5.

Heart failure requiring hospitalization and therapy with an inotropic agent, vasodilator, ACE inhibitor, increased diuretic dose, ultra filtration or dialysis, OR

Stroke, defined as a permanent neurological deficit of at least 24 hours duration, attributed to stroke by the personal physician, requiring hospitalization and confirmation by radiographic imaging.

**"Probable" Cardiovascular Outcomes:**

Non-fatal myocardial infarction, defined by a clinical report from the investigator but lacking confirmation of elevated enzymes or EKG changes, OR

Non-fatal myocardial infarction, defined by centrally read ECG that documents a new myocardial infarction in comparison to the baseline ECG but without clinical event, OR

Stroke, defined as above but lacking confirmation by radiographic imaging

## BP Management

AASK participants who have not reached ESRD are encouraged to have their BP managed by AASK Cohort investigators and staff. The recommended approach to hypertension control, both initial medication and BP goal, is based on the results of the AASK trial. The initial drug is the ACEI, ramipril. A loop diuretic is the next step. Subsequent medications are beta-blocker, calcium channel blocker, centrally acting alpha adrenergic blocker, and direct vasodilators. Within each class, medications donated by manufacturers are preferentially used. In contrast to the AASK trial, in which the

medication algorithm was fixed, there is investigator latitude during the cohort phase. The BP goal is a systolic BP < 140 mmHg and diastolic BP < 90 mmHg. However, in certain clinical settings, for example, heavy proteinuria or diabetes, a lower BP goal may be warranted.[5]

## Analyses

The analytic approach depends on the point at which risk factors are collected and the types of risk factors and outcomes (see Figure, Tables 2 and 3).

### Clinical Outcomes

The association of risk factors with the clinical outcomes (renal or cardiovascular) will be evaluated with Cox regression models including predictor variables of interest and indicator variables for the six cells of the 2 x 3 factorial trial design. The Period 2 analyses will include a separate set of time-dependent indicator variables for the time period that the patient was actually assigned to the randomized intervention in order to allow for different relative risks during and after the randomized trial. Analyses of the composite outcomes G1 or S1 will be administratively censored at the end of the designated study period (i.e., the end of Periods 1, 2 or 3) or final loss of contact with the patient; analyses of G2 and S2 will be censored at these times and at death.

### GFR Slope

The association of risk factors with GFR (or eGFR) slope will be examined with mixed effects models containing fixed effects terms for the predictor variables of interest along with additional terms to control for differences in the mean GFR (or eGFR) slopes among the six cells of the 2 x 3 factorial design of the randomized trial. For Period 2, the latter terms will include interactions between the six cells and linear spline terms in time to allow for different mean slopes during the first three months of the randomized trial (to account for initial acute effects of the interventions), the subsequent follow-up of the randomized trial (the chronic phase of the trial), the period between the final assessment of the trial and the first assessment of the cohort (to account for a second acute effect on termination of the trial interventions), and the remaining follow-up period of the Cohort Study (the chronic phase of the Cohort Study). Period 1 and Period 3 analyses will include the terms from the Period 2 model which are relevant to the randomized trial (Period 1) or the cohort follow-up (Period 3), respectively.

A potential complication of the slope-based analyses is informative censoring from loss-to-follow-up due to death, dialysis, or dropout. If censoring is informative, the standard mixed effects models may give biased estimates. Therefore, the results of the standard mixed effects models will be compared to extensions of these models which account for informative censoring. If substantial bias is identified for important predictor variables, informative censoring models will be used in place of the standard mixed effects models.

### Sample Size and Power

Of the 1,094 randomized participants, 263 died or reached ESRD by September 30, 2001. We anticipate that an additional 154 participants will be lost-to-follow-up or unwilling to participate in the AASK Cohort Study. Hence, the projected sample size is approximately 675.

Table 4 provides the projected numbers of events for each composite outcome, as the associated projected minimum detectable treatment effects (with 80% or 90% power based on an alpha level of 0.05, 2-sided test) for increases in risk associated with (1) a dichotomous risk factor with 50% prevalence, (2) a dichotomous risk factor with 20% prevalence, and (3) a 1-standard deviation change in a continuous risk factor that is linearly related to the log-transformed relative risk. The power calculations correspond to unadjusted risk ratios.

# Table 4: Minimum Detectable Increases in Relative Risk of Renal Composite Clinical Outcomes in Time-to-Event Analyses

| Period | Outcome* | Number Of Outcomes | Minimum Detectable Effect Sizes | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 80% Power | | | 90% Power | | |
| | | | Risk Factor With 50% Prevalence | Risk Factor With 20% Prevalence | 1 SD Δ in Quantitative Variable | Risk Factor With 50% Prevalence | Risk Factor With 20% Prevalence | 1 SD Δ in Quantitative Variable |
| Period 1 AASK Trial Only | ESRD, GFR Evt or death | 340 | 35% | 46% | 16% | 42% | 55% | 19% |
| | ESRD, GFR Evt | 263 | 41% | 54% | 19% | 49% | 64% | 22% |
| | ESRD or death | 249 | 43% | 56% | 19% | 51% | 67% | 22% |
| Period 2 AASK Trial + Cohort | ESRD, Scr Evt or death | 530 | 28% | 36% | 13% | 33% | 42% | 15% |
| | ESRD, Scr Evt | 413 | 32% | 41% | 15% | 38% | 49% | 17% |
| | ESRD or death | 452 | 30% | 39% | 14% | 36% | 46% | 16% |
| Period 3 AASK Cohort Only | ESRD, Scr Evt or death | 210 | 47% | 62% | 21% | 56% | 75% | 25% |
| | ESRD, Scr Evt | 173 | 53% | 70% | 24% | 64% | 85% | 28% |
| | ESRD or death | 176 | 53% | 69% | 23% | 63% | 84% | 28% |

*** See Table 2 for definitions of outcomes. ESRD, End Stage Renal Disease. GFR Evt, event defined by a reduction in glomeular filtration rate (GFR). Scr Evt, event defined by a doubling of serum creatinine.**

The following two examples illustrate the power calculations. Consider analyses done in Period 3 that compare non-dippers (individuals with < 10% BP decline from daytime to nighttime on ambulatory BP monitoring) to dippers (individuals with > 10% BP decline). If 50% of AASK participants are non-dippers, the study should have 80% power to detect a 47% or greater increase in the rate of composite endpoint of doubling of serum creatinine, ESRD, or death for non-dippers compared to dippers. As a second example, consider a Period 3 analysis relating the same composite outcome to serum total cholesterol, which has a standard deviation of ~ 45 mg/dL. This analysis should have 80% power to detect a 21% or greater increase in the event rate per one standard deviation (45 mg/dl) difference in total serum cholesterol.

## Discussion

The incidence and prevalence of hypertensive ESRD are relentlessly increasing, despite evidence from national surveys that rates of BP-related cardiovascular disease are declining. In view of the substantial public health burden of hypertensive kidney disease, particularly among African-Americans, and evidence that the condition is progressive, even among persons with well-controlled and appropriately treated hypertension, efforts to understand the determinants of disease progression are a high national priority.

The AASK Cohort Study is well-positioned to accomplish this task. First, this study is, to our knowledge, the only cohort study that specifically focuses on progression of kidney disease in African Americans with hypertensive kidney disease. Second, participants in the Cohort Study are extremely well-characterized. Baseline data on many exposures, including extensive medical history, detailed medication records, and numerous laboratory measurements, are already available, as is a bank of biological specimens. Third, the study is enriched with people who have progressive disease. To date, more than 300 persons have had a major decline in renal function, ESRD, or death. If another 200 outcomes occur during the Cohort Study, there will be > 500 incident ESRD cases, a number that vastly exceeds the incidence of all-cause ESRD cases in most population-based cohort studies, few of which enrolled large numbers of African-Americans. Fourth, the long duration of follow-up (9 to 12 years across trial and cohort phases) should allow us to identify and characterize persons with slow, but clinically important, renal disease progression.

Design considerations included selection of exposures and outcomes, and the approach to anti-hypertensive therapy. The number of candidate risk factors is vast. In this setting, we focused on a few biologically plausible factors. Salient new risk factors include markers of inflammation, diurnal BP from ambulatory BP, measurements of LV function and structure from trans-thoracic echocardiography, and a battery of psychosocial questionnaires. Specimens of urine, blood, and fingernails are collected and stored to assess the potential impact of other risk factors (e.g., heavy metals from fingernails). For cost and logistic considerations, we decided to estimate GFR from creatinine-based formula[4] rather than measure GFR from $^{125}$I-iothalamate clearance.

A major design consideration pertained to anti-hypertensive drug therapy. In the end, we decided to offer anti-hypertensive drug therapy to all cohort participants. Provision of such therapy has scientific, practical, and ethical roles. The scientific role is to directly control, rather than statistically adjust for, two of the major determinants of kidney disease progression (treatment of hypertension and use of renoprotective, antihypertensive medication). The practical role is to promote retention of individuals who otherwise might not participate in the Cohort Study after the trial ends. The ethical role is to avoid the situation of studying the impact of inadequately treated hypertension among individuals who received excellent care in the trial yet have inadequate resources to cover their own care after the trial ends.

In summary, results from the AASK Cohort Study should greatly enhance our understanding of the risk factors and processes that determine the progression of kidney disease. Such results might eventually lead to new strategies that delay or prevent ESRD.

## Acknowledgements

The authors extend their deep and sincere appreciation to the participants for their time and their extraordinary commitment to the AASK trial and now the AASK Cohort Study. The authors also acknowledge all members of the AASK Collaborative Research Group, which includes investigators and staff from 21 clinical centers, the Data Coordinating Center, and the primary sponsor, the National Institute of Diabetes and Digestive and Kidney Diseases. The 21 clinical centers are located at Case Western Reserve University, Emory University, Harbor-UCLA Medical Center, Harlem Hospital Center, Howard University, Johns Hopkins Medical Institutions, Martin Luther King, Sr. - Charles R. Drew Medical Center, Medical University of South Carolina, Meharry Medical College, Morehouse School of Medicine, Mount Sinai School of Medicine, Ohio State University, Rush Presbyterian St. Luke's Medical Center, University of Alabama at Birmingham, University of California at San Diego, University of Florida, University of Miami, University of Michigan, University of Southern California, University of Texas Southwestern Medical Center, and Vanderbilt University. The Data Coordinating Center is part of the Cleveland Clinic Foundation, which is also the site of the Central Biochemical Laboratory and the GFR Laboratory.

In addition to our primary sponsor, the authors gratefully acknowledge financial support from the Office of Research in Minority Health, and medication and financial support from Pfizer Inc, Astra-Zeneca Pharmaceuticals, and King Pharmaceuticals, Inc. The following NIH institutional grants also provided support: RR-00080, RR-00071, RR00032, RR1 1145, RR00827, RR00052, RR1 1104, and DK 2818.

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# Appendix E. AASK Cohort Study Informed Consent Form

**INFORMED CONSENT** for Subject's Name: _____ Date:

**Institution Name:**
**Address:**
**Telephone:**
**Fax:**
**Project Title:**

## African American Study of Kidney Disease and Hypertension (AASK) Cohort Study

(A project sponsored by the National Institutes of Health to study the role of high blood pressure and kidney disease in African-Americans)

**CONSENT TO PARTICIPATE IN RESEARCH.**

AASK Cohort Study — Template for Consent Form

You are asked to participate in a research study. You have been asked to participate in this study because you were a participant in the African American Study of Kidney Disease and Hypertension or AASK clinical trial. We expect xx people to participate in this study at XXX University and about 750 people throughout the nation. Your participation in this study is entirely voluntary. Please read the information below. Then ask questions about anything you do not understand before deciding whether or not to participate.

**BACKGROUND**
The kidneys normally get rid of body wastes by putting them into the urine. When kidney damage gets bad enough, a person cannot live without being treated with a kidney transplant or kidney machine (dialysis) to remove body wastes. High blood pressure is a common cause of kidney damage and is even more common in African Americans. This study will help us to understand why kidney disease gets worse in some people and not in others.

**PURPOSE OF THE STUDY:**
The purpose of this study is to find out:

a. What factors increase the chance of your kidney disease getting worse?
b. What are the long-term effects of the blood pressure medications used in AASK on your kidneys?
c. What other medical problems (such as heart disease) happen to people who have kidney disease and high blood pressure

**INFORMED CONSENT** for Subject's Name: _____ Date: _____

**You will be eligible to join this study if:**

You participated in the AASK clinical trial.

**WHAT YOU WILL DO IN THIS PROJECT**

There will be 2 main visits each year and 2 to 4 other visits to manage your blood pressure. On average, there will be one visit every 2 to 3 months. You may need to come more often for blood pressure checks and medication changes if your pressure is very high or low, or if your kidney function is getting worse. Also, to improve our data, we may ask some people to repeat a visit. At the main two visits, you will complete questionnaires about your health, have blood drawn (about 3 tablespoons), and have your blood pressure and weight measured. Your blood pressure medications will be adjusted to control your blood pressure. Once a year, we will get an EKG of your heart and will collect fingernail clippings; we also ask you to collect urine over a 24 hour period. A test that uses sound to check your heart (echocardiogram) will be done at the beginning of the study, two years later and at the end of the study. A test that measures your blood pressure every 30 minutes for 24 hours (ambulatory blood pressure) will also be done at the beginning of the study, two years later and at the end of the study. The entire follow-up period will last approximately 5 years. The main visits will last about an hour. The other visits will last 30 minutes. The following table summarizes the items to be collected at each visit.

| **Typical schedule of visits each year for participants who have not reached dialysis** | | | | |
|---|---|---|---|---|
| **Item** | **Visit 1(initial)** | **Visit 2 (month 3)** | **Visit 3 (month 6)** | **Visit 4 (month 9)** |
| Informed consent (just year 1) | X | | | |
| Blood pressure | X | X | X | X |
| Medication and health questionnaires | X | X | X | X |
| Blood drawing | X | X (just year 1) | X | |
| 24-hour Urine | X | | | |
| Finger nail clippings | X | | | |
| Electrocardiogram | X | | | |
| | | | | |
| Echocardiogram/48 hour BP | First, third, and fifth years | | | |
| 24-hr ABPM | Once in first, third, and fifth years | | | |

**INFORMED CONSENT** for Subject's Name: _____ Date: _____

If you develop severe kidney failure and need dialysis or a kidney transplant, we will still ask you to make visits twice each year. However, we will not manage your blood pressure; your kidney doctor will manage your blood pressure. We will ask you to complete questionnaires. Approximately three tablespoons (45 cc) of blood will be drawn at each visit. We may get additional information about hospitalizations and medications from your doctor. The following table summarizes the items to be collected at each visit if you develop kidney failure.

| **Typical schedule of visits each year for participants who have reached dialysis** | | |
|---|---|---|
| **Item** | **Visit 1 (initial)** | **Visit 2 (month 6)** |
| Medication and health questionnaires | X | X |
| Blood drawing (stored specimens) | X | X |
| Finger Nail Clippings | X | |
| Electrocardiogram | X | |
| Echocardiogram/48 hr BP | First, third and fifth years | |
| 24-hr ABPM | T in first year, once in third and fifth years | |

The next section provides more information about the types of information that we collect in this study.

Blood Pressure: Blood pressure will be measured by trained, certified staff. For this study, we want to manage your blood pressure. However, if you want your own physician to manage your blood pressure, we still ask you to attend the two main visits each year. Based on the AASK trial, our goal will be to control your blood pressure to less than 140/90 mmHg. We will start with ramipril, which was the most effective medication used in the AASK trial. Additional medications may be needed to control your blood pressure.

Questionnaires At each visit, we will ask you to complete questionnaires about your health, your medications, and recent hospitalizations.

Blood Drawing: Twice a year, blood will be drawn. Approximately three tablespoons (45 cc) of blood will be drawn on each visit. During the first year, blood will be drawn one extra time. The blood will be used to measure several items such as your kidney function, blood sugar, and cholesterol. Some blood will be frozen and stored for future use. We would like to get information about your genes; a separate consent form describes this part of the study.

24-Hour Urine Collection: Once each year, we will ask you to collect a urine specimen over a 24-hour period.

**INFORMED CONSENT** for Subject's Name: _____ Date: _____

Fingernails: Fingernail clippings will be collected once each year. You will be asked to trim each of your 10 fingers with a nail clipper (to be provided).

Electrocardiogram: Once each year, an electrocardiogram (EKG) of your heart will be obtained.

Echocardiography: In the first, third and fifth year, an echocardiogram will be obtained. This is a test that takes pictures of your heart using sound. It is like a x-ray but there is no radiation. This study takes about 20 minutes and gives information about how well your heart is functioning.

Ambulatory BP Monitoring: In the first, third and fifth year, a 24 hour ambulatory blood pressure recordings will be obtained. This requires you to wear a special blood pressure monitor for 24 hours and then bring it back. The monitor measures and records your blood pressure about every 30 minutes for 24 hours during the day and night.

**POTENTIAL RISKS AND DISCOMFORTS**

Blood drawing: Bruising of the arm where blood is taken (common), and infection or clotting of the vein (very rare). Also, you may experience temporary pain from the blooding drawings.

Medication-related side effects: You may develop medication-related side effects (e.g. fatigue, swelling, cough, itching or problems with your sexual function). However, you will be monitored for the occurrence of these and other side-effects. The medication will be reduced or stopped if side effects become a problem. It is always possible that some side effect might occur that has never occurred in anyone before.

Ramipril has caused swelling (angioedema) of the face, lips, tongue, throat and even the entire body. If this occurs go to the emergency room immediately. Ramipril may cause a cough. Ramipril lowers blood pressure and can cause your blood pressure to go too low. This may cause dizziness or feeling faint. Ramipril increases serum potassium and can cause potassium levels to go too high. Rarely, Ramipril has been associated with low white blood cell counts, liver problems. Ramipril should not be used during pregnancy. If you intend to become pregnant, you must tell us, and we will change your medication. If Ramipril is newly started, it is recommended you return in a few weeks to check your blood tests for kidney function, liver function, potassium and white blood cell count.

Fluid pills (furosemide or HCTZ) are commonly used to control blood pressure in persons with hypertension and kidney disease. Common side effects of fluid pills include low potassium levels, higher uric acid levels and gout, low blood pressure, rash, and problems with your sexual function (impotence).

A beta-blocker may be used if the ramipril and fluid pills do not control your blood pressure. Beta-blockers are contraindicated for patients with asthma or emphysema, or in patients with certain findings on EKG (second or third degree heart block). It can cause dizziness, getting weak easily (fatigue), depression, wheezing, cold extremities, skin rashes, worsening leg pains with walking (claudication), problems with your sexual

**INFORMED CONSENT** for Subject's Name: _____ Date: _____

function (impotence) and sleep disturbances. Other potential problems include slow heart rate (bradycardia), heart failure or new heart findings seen on EKG (second or third degree heart block).

Sometimes other medications may be needed to control your blood pressure. In that situation, we will provide information about common or serious side effects of these other medications.

Fingernail collections: You will be instructed how to trim your fingernails. There is a slight risk of bleeding and infection whenever a person trims their fingernails
Ambulatory BP Monitoring: Blood pressure readings may be uncomfortable and may wake you up at night when it measures your blood pressure.
Echocardiogram: This test takes pictures of your heart using sound. This test uses no radiation.

**POSSIBLE BENEFITS TO YOU:**
First, you may have better control of your blood pressure and maybe slow down or stop your kidney damage due to your high blood pressure.
Second, the questionnaires may lead to the early diagnosis of some other disease(s) that should be treated.
Third, you may learn more about your overall health and ways to change your diet and lifestyle to help you live longer
At your request, we can provide your personal health care provider with a copy of test results that might be useful for your medical care. However, most of the study tests are used just for research purposes; because these tests have uncertain importance, we will not make these tests routinely available.

**POSSIBLE BENEFITS TO SOCIETY:**
This study may help doctors learn more about kidney failure from high blood pressure and how to treat it better.
This study may help doctors learn what factors (such as high cholesterol, 24 hour blood pressure levels, family history of kidney disease) increase the chance of your kidney disease getting worse?
This study may also help doctors learn what other medical problems (such as heart disease) happen to people who have kidney disease and high blood pressure

**PAYMENT FOR PARTICIPATION:**
To compensate you for your time and transportation expenses, you will be provided XXX

**ALTERNATIVES TO PARTICIPATION:**
Not participate. You can have your hypertension or kidney disease followed in the XXX University clinic or your doctor's office.

**INFORMED CONSENT** for Subject's Name: _____ Date: _____

**FINANCIAL OBLIGATION:**
There will be no cost to you for your insurance company for participating in this study. However you or your insurance company will be responsible for your routine medical care and medications.

**EMERGENCY CARE AND COMPENSATION FOR INJURY:**
You participate in this research at your own risk. XXX University has not set aside funds for compensation or payment of research related injuries. You are not waiving any legal claims, rights or remedies because of your participation in this research study.

**PRIVACY AND CONFIDENTIALITY:**
Members of the research team and, if appropriate your physicians and nurses will know that you are a research subject. No information about you, or provided by you during the research, will be disclosed to others without your written permission, except:
if necessary to protect your rights or welfare (for example, if you are injured and need emergency care); or
if required by law (i.e., child abuse, elder abuse).
It is intended that results of this study be reported in medical or scientific journals and/or medical conferences so that the medical community and patients everywhere may benefit from this study. However, no information that personally identifies you will be published or released to non-study personnel except as specifically required by law. All information pertaining to this study will be kept in a locked file with access limited to study personnel only. The National Institutes of Health may inspect the study records according to the law. As a result, they may see your name; but they are bound by rules of confidentiality not to reveal your identity to others.

**INQUIRIES**
You may ask questions about any part of the study that you do not understand. You may contact Drs. x,y,z to discuss concerns or ask questions at (phone #).

**PARTICIPATION AND WITHDRAWAL**
Your participation in this research is VOLUNTARY. If you choose not to participate, that will not affect your relationship with the XXX University, or your right to health care or other services to which you are otherwise entitled. If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without prejudice to your future care at the XXX University.

**WITHDRAWAL OF PARTICIPATION BY THE INVESTIGATOR**

The investigator may withdraw you from participating in this research if circumstances arise which warrant doing so. If you experience serious side effects or if you become ill during the research, you may have to drop out, even if you would like to continue. The

**INFORMED CONSENT** for Subject's Name: _____ Date: _____

investigator, Dr. xxx, will make the decision and let you know if it is not possible for you to continue. The decision may be made either to protect your health and safety, or because it is part of the research plan that people who develop certain conditions may not continue to participate.

**IDENTIFICATION OF INVESTIGATORS**
In the event of a research related injury or if you experience an adverse reaction, please immediately contact one of the investigators listed below. If you have any questions about the research, please feel free to contact Drs x,y or Nurse z at phone #. If it is an emergency and after hours you can reach Dr. x at phone # or call at phone# for the XXX University Emergency Room.

**NEW FINDINGS**
During the course of the study, you will be informed of any significant new findings (either good or bad) that might cause you to change your mind about continuing in the study. If new information is provided to you, your consent to continue participating in this study will be re-obtained.

**BY SIGNING THIS FORM, I WILLINGLY AGREE TO PARTICIPATE IN THE RESEARCH IT DESCRIBES.**

_____
Name of Subject

_____
Name of Legal Representative *(if not applicable, delete signature lines and references to legal representation)*

_____
Signature of Subject or Legal RepresentativeDate

**INFORMED CONSENT** for Subject's Name: _____ Date: _____

**SIGNATURE OF INVESTIGATOR**

I have explained the research to the subject or his/her legal representative, and answered all of his/her questions. I believe that he/she understands the information described in this document and freely consents to participate.

_____
Name of Investigator

_____
Signature of Investigator Date (must be the same date as subject's)

**SIGNATURE OF WITNESS (*If required)***

My signature as witness certified that the subject or his/her legal representative signed this consent form in my presence as his/her voluntary act and deed.

_____
Name of Witness

_____
Signature of Witness Date (must be the same date as subject's)

**SIGNATURE OF PRIMARY PHYSICIAN**

I certify that I am this patient's primary physician at this time, I am aware of her participation in this research project, and I am not aware of any medical contraindication to her participation other than the risks described above.

Primary Physician or Designee _____ Date

# Appendix F. AASK Cohort Genetics Consent Template

**MOUNT SINAI SCHOOL OF MEDICINE**
**CONSENT FOR RESEARCH**

GCO # 99-577ME*

## PART I - RESEARCH PARTICIPANT INFORMATION SHEET:

### A. PURPOSE OF THE STUDY:

You are asked to participate in a research study. The purpose of the study is to determine whether certain genes influence blood pressure, kidney disease and heart disease. You qualify for this study because you have high blood pressure, have kidney disease and participated in the African American Study of Kidney Disease and Hypertension (AASK) study.

### B. DESCRIPTION OF THE RESEARCH:

We will take one blood sample (4 teaspoons) from you. We will remove DNA (the material that genes are made of) from the blood samples and will preserve (immortalize) some of the blood cells for future use or for additional DNA. DNA from the blood samples will be analyzed for the presence of different forms of genes. We will then find out if any of these genes are associated with blood pressure, kidney disease or heart disease.

Your samples will be labeled with your AASK number and AASK name code. It will therefore ‘be possible for study investigators to identify you or contact you. For instance, we may contact you about future studies that involve genes. Your DNA and cells will be stored indefinitely. Some of the DNA may be used in future studies or shared with other investigators who are performing similar studies.

### C. COSTS/REIMURSEMENTS:

There will be no cost to you for participation in this study. There will be XX reimbursement for participation.

_____

**Init. _____**

***For IRB Official Use Only***

This Consent Document is approved for use by Mount Sinai’s Institutional Review Board (IRB)

From:_____To:_____

**MOUNT SINAI SCHOOL OF MEDICINE**
**CONSENT FOR RESEARCH**

## D. POTENTIAL RISKS AND DISCOMFORTS

The blood drawing may cause very brief discomfort, and it is possible that a small bruise or, very uncommonly, an infection may develop at the site of needle entry.

However, we will draw the blood as part of the blood draws scheduled for the AASK study so that you will not have to undergo an additional needle stick.

## E. POTENTIAL BENEFITS:

The genetic studies will not directly benefit you. If a close relationship between a gene and damage to the heart or the kidney is found, future research may lead to a screening test to predict who is at risk for heart or kidney problems. If this is the case, such screening may lead to early detection and/or better treatment of high blood pressure, kidney disease or heart disease.

All information pertaining to this study including the genetic information will remain confidential. At present, this genetic information is used just for research purposes. If the information could be used for clinical purposes as well, we will make this information available to you.

## F. ALTERNATIVES TO PARTICIPATION (where applicable):

The alternative is not to participate.

## C. CONFIDENTIALITY:

Your identity as a participant in this research study will be kept confidential in any publication of the results of this study. Your medical record in connection with this study will be kept confidential to the extent permitted by law. However, your medical record may be reviewed by government agencies or the agency sponsoring this research, if required by applicable laws or regulations.

**Init. _____**

***For IRB Official Use Only***

This Consent Document is approved for use by Mount Sinai's Institutional Review Board (IRB)

From:_____ To:_____

**MOUNT SINAI SCHOOL OF MEDICINE**
**CONSENT FOR RESEARCH**

## H. COMPENSATION/TREATMENT:

If you believe that you have suffered an injury related to this research as a participant in this study, you should contact Dr. Michael Lipkowitz at telephone number 212-241-2264

## I. VOLUNTARY PARTICIPATION: I

Participation in this study is voluntary. If you decide not to participate, this will not affect your ability to receive medical care at Mount Sinai or to receive any benefits to which you are otherwise entitled.

Any new information that develops during this study, which might affect your decision to participate, will be given to you immediately.

A signed copy of this consent form will be given to you.

## J. TERMINATION OF PARTICIPATION:

You may discontinue participation in the study at any time without penalty or loss of benefits to which you are otherwise entitled.

## K. CONTACT PERSON(S):

If you have any questions, at any time, about this research, please contact Dr. Michael Lipkowitz, at telephone number 212-241-2264. If you still have questions you may discuss them with a member of the Institutional Review Board (the committee which oversees research at Mount Sinai School of Medicine) at telephone number (212) 659-8980.

_____

**Init. _____**

***For IRE Official Use Only***
This Consent Document is approved for use by Mount Sinai's Institutional Review Board (IEB)

From:_____ To:_____

**MOUNT SINAI SCHOOL OF MEDICINE**
**CONSENT FOR RESEARCH**

GCO # 99-577ME*
Authorization to Participate in Research

**This form must be signed by the participant/surrogate and the investigator/delegate.**

Participant:_____ Date: _____
(PRINT NAME)

1. I hereby volunteer to participate in a research program under the supervision of Dr. Lipkowitz and his/her associates at Mount Sinai School of Medicine.

2. I acknowledge that I have read, or had explained to me in a language I understand, the attached consent document and that Dr. Lipkowitz has explained to me the nature and purpose of these studies. This explanation included a description of the parts of the study that are experimental, the possible discomforts, symptoms, side effects and risks that I might reasonably expect, and the possible complications, if any, that I might reasonably experience from both known and unknown causes as a result of my participation in these studies. I have had the opportunity to ask questions I had about the study and all of the questions I asked were answered to my satisfaction.

3. I understand that I am free to withdraw this authorization and to discontinue my participation in these studies any time. The consequences and risks, if any, of withdrawing from the study while it is ongoing have been explained to me. I understand that such withdrawal will not affect my ability to receive medical care to which I might otherwise be entitled.

4. I confirm that I have read, or had read to me, this entire authorization and that all blanks or statements that require completion were in fact, properly completed before I signed this authorization.

Research Subject/Surrogate:_____
(Signature)

Name:_____
(Print Name)

Relationship:_____
(If signed by surrogate))

_____

**Init._____**

*For IRB Official Use Only*
This Consent Document is approved for use by Mount Sinai's Institutional Review Board (IRB)
From:_____To:_____

**MOUNT SINAI SCHOOL OF MEDICINE**
**CONSENT FOR RESEARCH**

Authorization to Participate in Research *(continued)*

*For subjects who are not able to read this consent document themselves, the following must be completed:*

I confirm that I have accurately translated and/or read the information to the subject:

Witness:_____
(SIGNATURE)

Name: _____
(PRINT NAME)

Address:_____
NUMBER AND STREET CITY STATE ZIPCODE

I have fully explained to the above patient/relative/guardian the nature and purpose of the foregoing drugs, devices or procedures, possible alternative methods of treatment which might be advantageous, the benefits reasonably to be expected, the attendant discomforts and risks involved, the possibility that complications may arise as a result thereof and the consequences and risks, if any, which might be involved in the event the

_____

**Init._____**

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From:_____To:_____

**MOUNT SINAI SCHOOL OF MEDICINE**
**CONSENT FOR RESEARCH**

patient/relative/guardian hereafter decides to discontinue such treatment. I believe that the above patient/relative/guardian understands the nature, purposes, benefits, and risks of participation in this research. I have also offered to answer any questions the above patient/relative/guardian might have with respect to such drugs, devices or procedures and have fully and completely answered all such questions.

_____
(Signature of Principal Investigator/Delegate) (Date)

_____
(Print Name) (Title)

_____

**Init._____**

***For IRB Official Use Only***
This Consent Document is approved for use by Mount Sinai's Institutional Review Board (IRB)
From:_____To:_____

*GCO Version* 2.2 *June 2000*

# Appendix G. Guidelines for Use of Biological Specimens in the AASK Trial and AASK Cohort Studies

## I. Overview

The AASK Biological Specimens Allocation (ABSA) Committee consists of members from the AASK Publications and Ancillary Studies Committee, the NIDDK, the Data Coordinating Committee (DCC) and the AASK Executive Committee. A catalog of all proposals/authors and reviewers will be the responsibility of Coordinating Center. The ABSA Committee will review all requests for biological specimens *every three months.*

An active AASK investigator must be involved as an investigator on each project. The AASK investigator may be either an AASK principal Investigator or co-Investigator. If a non-AASK investigator submits a proposal, at least one AASK investigator must be added as an investigator on the proposal. If a non-AASK investigator submits a proposal from a non-AASK affiliated institution, they must find, with the help of the ABSA committee, an AASK investigator willing to participate in the project. In the case where two very similar proposals are submitted with little distinction in scientific scope, the application submitted by an AASK investigator will be given priority.

The procedures for submitting a request for biological specimens, reviewing the proposals, and distributing the biological specimens are described below. Because the volume of biological specimens is limited, all meritorious requests cannot be approved.

## II. Request for Use of Biological Specimens

The request for specimens MUST contain the following information:

1. Biosketches of the Principal investigator and other co-investigators *(must be in NIH format)*
2. Abstract
3. Hypothesis to be tested
4. Background and significance (maximum of *two* pages)
5. Design-Methods-Key References (maximum of *four* pages)
6. Description of specimen request (maximum of *two* pages)
    a) Specific type(s) of samples
    b) Volume of each sample
    c) Time of sample collection (baseline vs. post-baseline) — Proposals that require baseline biological specimens (vs. post-baseline) must provide a strong rationale for use of the baseline specimens.
    d) Use of thawed vs. unthawed specimens - for blood and urine, proposals must indicate whether previously thawed specimens can be used. The use of unthawed specimens will require a strong rationale.
    e) Number of participants
    f) Type of storage—for urine, -20 or $-70^0$F
    g) Proposed laboratory that will perform the assays

h) DNA specimens — all proposals that require DNA must involve Dr. Lipkowitz at Mt. Sinai Medical Center in New York. His group has immortalized cells and has a data bank of DNA. See appendix for specific requirements regarding use of serum, plasma, DNA and urine

7. Need for other study data (e.g. baseline and/or follow-up data) and other study resources
8. Time table with key dates (grant submission, target date for receipt of specimens, and completion of study
9. Documentation of local IRB approval [required prior to release of specimens]
10. Agreement to return any unused biological specimens
11. Budgetary issues
    a) Source(s) of funding
    b) Draft budget that includes costs of shipping, assays and other costs identified by the coordinating center (e.g. costs of preparing data request and aliquoting specimens). For all request, applicants are advised to contact Dr. Gerald Beck.

    Gerald Beck, Ph.D.
    AASK Data Coordinating Center, Desk Wb-4
    Cleveland Clinic Foundation
    9500 Euclid Avenue
    Cleveland, Ohio 44195
    E-mail:- beckg@ccf.org

    For DNA requests, applicants should also contact Dr. Lipkowicz.

**III. The Review Process**

Submitted proposals will be reviewed by the ABSA Committee. This committee contains at least one representative from each of the following: the NIDDK, the AASK Executive Committee, the AASK Publications and Ancillary Studies Committee, and the AASK Data Coordinating Center. The names of the members of this committee will be available. Applicants can also recommend ad hoc reviewers for their proposal; however, the final decision regarding the review rests with the ABSA Committee.

All members will be responsible for reviewing all protocols. Two members of the committee, a primary and secondary reviewer, will be appointed by Gerald Beck from the DCC with input from the Committee, to critique each protocol for scientific merit and feasibility. They will be expected to summarize their findings and make a recommendation that will be submitted to Gerald Beck for dissemination to the committee. The Chair of the Committee will review all proposals, and will review the evaluations, and discuss the status with the ABSA committee before a vote is taken and a final recommendation made. These reviews need to be submitted within three weeks of receipt and before the next conference call that will discuss them. A quorum of the ABSA committee, including all reviewers of a protocol to be discussed should be available for calls upon which a decision will be made.

The criteria for review of specimen requests for determination of acceptability and determination of conflict of interest will be similar to those used by NIH peer reviews. Projects will be reviewed according to:

1. Significance and Applicability
Does this study address an important issue relevant to progression of kidney disease or its complications in African-Americans? If the aims of the application are achieved, how will scientific knowledge be advanced?

2. Scientific Approach
Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

3. Innovation
Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

4. Investigator
Is the investigator appropriately trained and well-suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers?

5. Environment
Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements?

6. Funding
Does this proposal have specific funding? Is the funding adequate to perform the work?

**Release of Biological Specimens**

Each group represented on the ABSA Committee will have a single vote. All decisions of the Committee will be determined by majority vote and the NIDDK Project Office will review all decisions by the Committee.

The Committee can approve a proposal for access to biological specimens, deny a proposal for access to biological specimens, or provisionally approve a proposal that is deemed likely meritorious but requires some additional changes before approval. A provisional approval will lapse six months after the initial Committee decision if no resubmission is made.

An investigator whose proposal fails to meet the criteria for access to biological specimens is entitled to constructive criticism about the proposal and resubmissions will be accepted. The decision of the Committee regarding access to biological specimens for a given proposal will be made available to the applicant within two weeks of the review. Proposals will be reviewed every three months.

Initial submissions to a funding agency that requires proof of access to AASK biological specimens will be considered and, if felt to be meritorious, a letter affirming the willingness of the AASK ABSA Biological specimens Committee to provide biological specimens will be provided for the submission.

The type and quantity of biological specimens requested may affect whether the request can be filled and how quickly this can be done. An investigator whose proposal is approved for biological specimens cannot be guaranteed immediate access to biological specimens.

The proposals that have been approved for access to biological specimens will receive biological specimens as follows.

The list of investigators awaiting biological specimens will be stratified by type of specimen (blood, urine DNA, and toe nails). For each, the priority will be determined only by the date placed on the approved list. In other words, the most recent investigator approved will be at the bottom of the list (for whatever type of biological specimens he/she requires). Once an investigator receives biological specimens, requests for additional biological specimens must be preceded by providing the Committee an update of the research progress and IRB approval, and then his/her name will be placed at the bottom of the list. All investigators receiving biological specimens need to submit an annual progress report to the DCC. Publication of results needs to follow the AASK Publications Policy.

Investigators who feel unfairly treated either in terms of denial of a proposal for investigation or receipt of biological specimens may address complaints to the NIDDK Project Officer for AASK.

# Appendix H. AASK Ancillary Studies Status (as of October 2001)

1. Robert Phillips, Mount Sinai
Role of Self Blood Pressure Monitoring in Management
of African Americans with Renal Dysfunction
Proposed: August 4, 1994
PAS: More information requested, August 24, 1994

2. Robert Phillips, Mount Sinai
Accuracy of Ambulatory Automatic Blood Pressure Measurements
Proposed: August 5, 1994
PAS: More information requested, August 24, 1994
Investigator: Study will not be pursued

3. Nancy Brown, Vanderbilt University
Collection of Genomic DNA from AASK Patients
Proposed: October 19, 1994
PAS: Tabled, November 23, 1994
(AASK policy on genetic studies needed)
Revised: September *25,* 1995
PAS: Not approved, November 28, 1995

4. Babatunde Olutade and Dallas Hall, Emory University
The Seroprevalence of Hantavirus Antibody Among Hypertensives with and without Renal Insufficiency
Proposed: November 8, 1994
PAS: More information requested, November 23, 1994

*5. Gary Friday/Michael Klibaner, Astra, USA; Robert Phillips, Mount Sinai
Harold Kennedy, Saint Anthony's Medical Center, Saint Louis
Effect of Drug Treatment on Heart Rate Variability in Hypertensive Patients with Mild to Moderate Renal Dysfunction
Proposed: March 20, 1995
Funding: Astra
PAS: Approved, March 29, 1995
Steering Committee: Approved, September 6, 1995
Investigators Call: Protocol discussion, December 18, 1995
Study Initiated: February, 1996

6. Roger London, Mount Sinai
Cost-Benefit of AASK Intervention
Proposed: February 9, 1995
PAS: More information requested, March 29, 1995

7. Daniel O'Conner, University of California, San Diego AASK Genotypic Determinants of Outcome
Proposed: August 20, 1995
PAS: Not approved, November 28, 1995

*8. Bracie Watson, Jr. and Denyse Thomley-Brown, University of Alabama Genetic Association of 11 13-Hydroxysteroid Dehydrogenase
Type 2 and Essential Hypertension
Proposed: September 28, 1995
PAS: Approved, November 28, 1995 (Samples will be from Lipkowitz - Study *#9)*
Steering Committee: Approved, January 23, 1996

*9. Michael Lipkowitz and Robert Phillips, Mount Sinai
Genetic Determinants of Hypertensive Nephropathy in African Americans
Proposed: October 1, 1995
PAS: Approved, November 28, 1995
Steering Committee: Approved, January 23, 1996
Modified Proposal: April 16, 1998
PAS: Approved, June 16, 1998

10. DeAnna Cheek, Medical University of South Carolina
Genetic Determinants of Renal Disease in AASK Patients
Proposed: October 1, 1995
PAS: Not approved, November 28, 1995

11. Jackson Wright, Case Western Reserve University
Association Between Phenotypic Alterations in Intracellular Sodium and It's Genetic Determinants in U.S. and Ugandan Blacks
Proposed: October 8, 1995
PAS: Not approved, November 28, 1995

* 12. Stephanie Ladson-Wofford and Lee Hebert, Ohio State University
Relationship between Renal and Cardiovascular Outcomes and Blood Pressure Control as Assessed by Ambulatory Blood Pressure Monitoring

Proposed: February 19, 1996
Funding: NIDDK
PAS: Approved in concept, March 4, 1996
Revised: July 28, 1997
PAS: Approved as pilot study, August 20, 1997
Steering Committee: Approved as pilot study, October *15,* 1997

*13. Kenneth Jamerson, University of Michigan
An Assessment of Factors that Influence the Decision of African Americans to Participate in Biomedical Research
Proposed: May 1, 1996
PAS: Approved in concept, September 6, 1996
Steering Committee: Approved, September 10, 1996

* 14. Andrew Todd and Robert Phillips, Mount Sinai
African Americans, Hypertension and Lead Exposure
Proposed: August 21, 1997
Funding: Submitted to NIDDK
PAS: Approved conditionally, January 29, 1998
Response from Investigator: February 8, 1998
Steering Committee: Approved, February 28, 1998

* 15. Richard Johnson, University of Washington
Osteopontin as a Predictor of Progression of Renal Disease in African Americans
Proposed: February 24, 1998
PAS: Not Approved, March 31, 1998
Revised: June 16, 1998
PAS: Approved, June 18, 1998

* 16. Agnes Fogo, Vanderbilt University
Morphometric Study and Types of Global Sclerosis
Proposed: May 14, 1998
PAS: Approved, June 11, 1998

*17. Leena Hiremath, Ohio State University
Frequency of Occurrence of T594M Variant in AASK and Its Contribution to ESRD
Proposed: May 12, 1998
PAS: Further input requested, June 11, 1998
Revised: September 16, 1998
PAS: Approved, November 24, 1998
Steering Committee: Approved, December 8, 1998

* 18. Betty Levell, Cornell University John Kusek, NLDDK
Domains of Quality of Life Not Measured by SF36
Proposed: February 9, 1999
PAS: Approved, March 2, 1999
Steering Committee: Approved, April 7, 1999

19. Janice Lea, Emory University
Determination of TGF-βLevels and Its Relationship with Blood Pressure and the Progression of Hypertensive Renal Disease
Proposed: July 1, 1999
PAS: Approved in concept, September 10, 1999
*Active or approved

*AASK/Publications/Ancillary/ancillarystatuslOOl.fr,n*

# Appendix I. AASK Publications and Presentations (as of December, 2002)

**(Prepared by the AASK Data Coordinating Center)**

## PAPERS

Agodoa L. African American Study of Kidney Disease and Hypertension (AASK)—clinical trial update. Ethnicity & Disease 8:249-253, 1998.

Agodoa LY, Appel L, Bakris GL et al. for the African American Study of Kidney Disease in Hypertension (AASK) Study Group: Effect of ramipril vs. amlodipine on renal outcomes in hypertensive nephrosclerosis: A randomized controlled trial. Journal of the American Medical Association. 285:2719-2728, 2001.

Lewis J, Agodoa L, Cheek D, Greene T, Middleton J, O'Connor D, Ojo A, Phillips R, Sika M, Wright J, Jr. for the AASK Study Group. Comparison of cross-sectional renal function measurements in African-Americans with hypertensive nephrosclerosis and of primary formulas to estimate GFR. American Journal of Kidney Diseases. 38:744-753, 2001.

Sica DA, Douglas JG. The African American Study of Kidney Disease and Hypertension (AASK) Trial: New findings. Journal of Clinical Hypertension. 3:244-51, 2001.

Kusek J, Greene P, Wang S-R, Beck G, West D, Jamerson K, Agodoa L, Faulkner M, Level B, and the AASK Study Group. Cross-sectional study of health-related quality of life in African Americans with chronic renal insufficiency: The African American Study of Kidney Disease and Hypertension (AASK) Trial. American Journal of Kidney Diseases. 39:513-24, 2002.

Wright JT, Agodoa L, Contreras G, Greene T, Douglas JG, Lash J, Randall O, Rogers N, Smith MC, Massry S and the AASK Study Group. Achieved blood pressure control in the African American Study of Kidney Disease and Hypertension (AASK). Archives of Internal Medicine. 162:1636-43, 2002.

Wright JT, Agodoa L, Appel L, Bakris G, Charleston J, Cheek D, Douglas-Baltimore J, Gassman J, Glassock R, Greene T, Hebert L, Jamerson K, Lewis J, Middleton J, Phillips R, Rostand S, Toto R and the AASK Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: Results from the AASK Trial. Journal of the American Medical Association. 288:2421-243 1. 2002.

Lea JP, Brown DT, Lipkowitz M, Middleton J and Norris K for the AASK Study Group. Preventing renal dysfunction in patients with hypertension: Clinical implications from the early AASK trial results. American Journal of Cardiovascular Disease. In Press, 2002.

Gassman J, Agodoa L, Bakris G, Beck G, Douglas J, Greene T, Jamerson K, Kutner M, Lewis J, Randall OS, Wang S and Wright JT for the AASK Study Group. Design and statistical aspects of the African American Study of Kidney Disease and Hypertension (AASK). Journal of the American Society of Nephrology. In Press, 2002.

Appel L, Agodoa L, Bakris G, Charleston J, Douglas J, Gassman J, Greene T, Jamerson K, Kusek J, Lewis JA, Middleton J, Miller ER, Lipkowitz M, Norris K, Phillips R, Rostand SG and Wright JT for the AASK Collaborative Research Group. The rationale and design of the AASK Cohort Study (AASK). Journal of the American Society of Nephrology. In Press, 2002.

## ABSTRACTS

From the AASK (Prepared by Cheek D, Bourgoignie J, Cleveland W, Kusek JW, Norris K, Wang SR). Blood pressure in screenees for the African American Study of Kidney Disease and Hypertension (AASK). American Journal of Hypertension. 10(4, Part 2); 79A, 1997.

From the AASK (Prepared by Greene P, Brooks D, Gassman JJ, Greene T, Hall Y, Kusek JW, Phillips R, Smith D, Wilkening B, and the AASK Study Group.) Pill counting and attainment of blood pressure goals in the African American Study of Kidney Disease and Hypertension (AASK). Controlled Clinical Trials. 18: 68S-69S, 1997.

From the AASK (Prepared by Hall WD, Wang SR, Kusek JW, Rogers N, Charleston J, Kopple J, Pogue V) African American Study of Kidney Disease and Hypertension (Full-Scale AASK): Baseline clinical and demographic characteristics of the randomized participants. Ethnicity & Disease. 7 (Suppl.): S1, 1997.

From the AASK (Prepared by Kusek JW, Levell B, Beck G, Jamerson K, Agodoa L, Faulkner M, Greene P, Milligan 5, Smith D). Baseline quality of life in the African American Study of Kidney Disease and Hypertension (AASK) Full-Scale Trial. Ethnicity & Disease. 7 (Suppl.): S2, 1997.

From the AASK (Prepared by Kutner M, Agodoa L, Gassman JJ, Glassock R, Greene T, Olutade B, Randall O). Design and statistical aspects of the African American Study of Kidney Disease and Hypertension (AASK). Ethnicity & Disease. 7 (Suppl.): S44, 1997.

From the AASK (Prepared by Wright JT, Jr., Bakris, GL, Douglas M, Gassman JJ, Kusek JW, Massry SG, Powers SN, Rostand SG). Baseline and achieved blood pressure in the

African American Study of Kidney Disease and Hypertension (AASK). Ethnicity & Disease. 7 (Suppl.): S1, 1997.

Cheek D, Lipkowitz M, Kopple J, Pogue V. Rostand S, Wang SR and the AASK Group. Risk factors for cardiovascular disease and history of stroke by region: Observations from the African American Study of Kidney Disease (AASK). Ethnicity & Disease. 8:279, 1998.

Kusek JW, Thompson R, Burgin L, Tisher C, Phillips R, Brittain K, Jaen L, Johnson F and the AASK Group. Successful use of state-funded public health clinics computerized chart review, and community liaison workers to recruit African Americans with renal diseases due to hypertension into a clinical trial. Ethnicity & Disease. 8:273, 1998.

Jamerson K, Gassman J, Greene, P. Hiremath L, Kusek J, Norris K, Thornley-Brown D and the AASK Group. African Americans have high rates of adherence to therapy in a clinical trial. Ethnicity & Disease. 8:274, 1998.

Phillips R, Agodoa L, Beck G, Lewis Breyer J, Coresh J, Massry S and the AASK Group. African-American women with hypertension and "normal" creatinine have significant renal dysfunction. Ethnicity & Disease. 8:272, 1998.

Wright JT Jr., Agodoa L, Cheek D, Greene T, Richardson A and the AASK Study Group. Achievement of blood pressure goals in patient subgroups of the African American Study of Kidney Disease and Hypertension (AASK). Ethnicity & Disease. 8:274, 1998.

Agodoa L, Miller ER, Brooks D, Gassman J, Ladson-Wofford S, Retta T, Rogers N and the AASK Study Group. Back titration of antihypertensive medications: The AASK Study experience. Journal of the American Society of Nephrology. 9: 138A, 1998.

Bakris G, Randall O, Rahman M, Lea J, Ward H, Massry S, Wang SR and the AASK Group. Associations between cardiovascular risk factors and glomerular filtration rate at baseline in the African American Study of Kidney Disease (AASK) trial. Journal of the American Society of Nephrology. 9: 139A, 1998.

Hebert LA, Appel L, Cleveland W, Greene T, Jamerson K, Kopple J, Pogue V and the AASK Study Group. Cigarette smoking is associated with lower glomerular filtration rate in African Americans with hypertensive nephrosclerosis. Journal of the American Society of Nephrology. 9: 149A, 1998

Lewis JB, Agodoa L, Cheek D, Greene T, Middleton J, O'Connor D, Wright J and the AASK Study Group. Estimation of GFR from serum creatinine in the African American Study of Kidney Disease and Hypertension (AASK). Journal of the American Society of Nephrology. 9:153A, 1998.

Phillips R, Faulkner M, Gassman J, Kusek J, Norris K, Thompson B, Thomley-Brown D and the AASK Study Group. Recruitment in the African American Study of Kidney Disease and Hypertension. Journal of the American Society of Nephrology. 9: 159A, 1998.

Rostand S, Beck G, Charleston J, Contreras G, Greene P, Herbert L, Kusek J, Wang SW and the AASK Study Group. Quality of life is positively related to level of GFR in subjects screened for the African American Study of Kidney Disease and Hypertension (AASK). Journal of the American Society of Nephrology. 9: 159A, 1998.

Srivastava A, Lipkowitz M, Cheek D, Middleton J, Kusek J, Beck G, Phillips RA and the AASK Study Group. Left ventricular hypertrophy is dependent on renal dysfunction in African Americans with hypertension. Journal of the American Society of Nephrology. 9:33lA, 1998.

Agodoa L, Douglas J, Gassman J, Kutner M, Wright J. for the AASK Study Group. The African American Study of Kidney Disease and Hypertension (AASK): Progress report. Journal of the American Society of Nephrology. 10: 152A, 1999.

Phillips R, Gadegbku, C, Lash J, Middleton J, Rostand S, Van Lente F, Wang S and the AASK Study Group. Low rates of adequate lipid management in African Americans with or at risk for renal disease. Journal of the American Society of Nephrology. 10: 177-178A, 1999.

Pogue V, Bakris G, Cheek D, Greene T, Lea J, Randall O, Toto R and the AASK Study Group. Association of pulse pressure with glomerular filtration rate: A cross-sectional study of 2,037 African Americans. Journal of the American Society of Nephrology. 10: 178A, 1999.

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Lash JP, Agodoa L, Brittain K, Cheek D, Contreras G, Gassman J, Miller ER, Randall O, Thomley-Brown D and the AASK Study Group. ACE-inhibitors and calcium channel blockers are safe and well tolerated in patients with chronic renal insufficiency: Interim results of the AASK Study. Journal of the American Society of Nephrology. 12:219A, 2001.

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Miller ER III, Appel LI, Cheek D, Greene T, Kusek JW, Lash J, Schulman G and the AASK Study Group. Ramipril and amlodipine-based therapy to prevent proteinuria: Results from the African American Study of Kidney Disease (AASK). Journal of the American Society of Nephrology. 12:469A, 2001.

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## PRESENTATIONS

From the AASK (Prepared by Cheek D, Bourgoignie J, Cleveland W, Kusek JW, Norris K, Wang SR). Blood pressure in screenees for the African American Study of Kidney Disease and Hypertension (AASK). American Society of Hypertension Twelfth Scientific Meeting, San Francisco, California, May 27-31, 1997.

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From the AASK (Prepared by Hall WD, Wang SR, Kusek JW, Rogers N, Charleston J, Kopple J, Pogue V) African American Study of Kidney Disease and Hypertension (Full-Scale AASK): Baseline clinical and demographic characteristics of the randomized participants. Twelfth International Interdisciplinary Conference on Hypertension in Blacks, London, England, July 20-24, 1997.

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Phillips RA, Brittain K, Charleston J, Johnson F, Kusek JW, Richardson A, Thompson R for the AASK Group. Increased demands in recruitment effort from the Pilot to the Full-Scale Phase in the African American Study of Kidney Disease and Hypertension (AASK). American Society of Hypertension Thirteenth Scientific Meeting, New York, New York, May 13-16. 1998.

Cheek D, Lipkowitz M, Kopple J. Pogue V, Rostand S, Wang SR and the AASK Group. Risk factors for cardiovascular disease and history of stroke by region: Observations from the African American Study of Kidney Disease (AASK). Thirteenth International Interdisciplinary Conference on Hypertension in Blacks, Charleston, South Carolina, July 12-18,1998.

Kusek JW, Thompson R, Burgin L, Tisher C, Phillips R, Brittain K, Jaen L, Johnson F and the AASK Group. Successful use of state-funded public health clinics computerized chart review, and community liaison workers to recruit African Americans with renal disease due to hypertension into a clinical trial. Thirteenth International Interdisciplinary Conference on Hypertension in Blacks, Charleston, South Carolina, July 12-18, 1998.

Jamerson K, Gassman J, Greene, P. Hiremath L, Kusek J, Norris K, Thornley-Brown D and the AASK Group. African Americans have high rates of adherence to therapy in a clinical trial. Thirteenth International Interdisciplinary Conference on Hypertension in Blacks, Charleston, South Carolina, July 12-18, 1998.

Phillips R, Agodoa L, Beck G, Lewis Breyer J, Coresh J, Massry S and the AASK Group. African-American women with hypertension and "normal" creatinine have significant renal dysfunction. Thirteenth International Interdisciplinary Conference on Hypertension in Blacks, Charleston, South Carolina, July 12-18, 1998.

Wright JT Jr., Agodoa L, Cheek D, Greene T, Richardson A, and the AASK Group. Achievement of blood pressure goals in patient subgroups of the African American Study of Kidney Disease and Hypertension (AASK). Thirteenth International Interdisciplinary Conference on Hypertension in Blacks, Charleston, South Carolina, July 12-18, 1998.

Agodoa L, Miller ER, Brooks D, Gassman J, Ladson-Wofford S, Retta T, Rogers N and the AASK Study Group. Back titration of antihypertensive medications: The AASK Study experience. American Society of Nephrology 31st Annual Meeting, Philadelphia, Pennsylvania, October 25-28, 1998.

Bakris G, Randall O, Rahman M, Lea J, Ward H, Massry S, Wang SR and the AASK Group. Associations between cardiovascular risk factors and glomerular filtration rate at baseline in the African American Study of Kidney Disease (AASK) trial. American Society of Nephrology 31st Annual Meeting, Philadelphia, Pennsylvania, October 25-28, 1998.

Hebert, LA, Appel L, Cleveland W, Greene T, Jamerson K, Kopple J, Pogue V and the AASK Study Group. Cigarette smoking is associated with lower glomerular filtration rate in African Americans with hypertensive nephrosclerosis. American Society of Nephrology 31st Annual Meeting, Philadelphia, Pennsylvania, October 25-28, 1998.

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Phillips R, Faulkner M, Gassman J, Kusek J, Norris K, Thompson B, Thornley-Brown D and the AASK Study Group. Recruitment in the African American Study of Kidney Disease and Hypertension. American Society of Nephrology 31st Annual Meeting, Philadelphia, Pennsylvania, October *25-28,* 1998.

Rostand S, Beck G, Charleston J, Contreras G, Greene P. Herbert L, Kusek J, Wang SW and the AASK Study Group. Quality of life is positively related to level of GFR in subjects screened for the African American Study of Kidney Disease and Hypertension (AASK). American Society of Nephrology 31st Annual Meeting, Philadelphia, Pennsylvania, October 25-28, 1998.

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Agodoa L, Douglas J, Gassman J, Kutner M, Wright J. for the AASK Study Group. The African American Study of Kidney Disease and Hypertension (AASK): Progress report. - American Society of Nephrology 32nd Annual Meeting, Miami Beach, Florida,

November 5-8, 1999.

Phillips R, Gadegbku, C, Lash J, Middleton J, Rostand 5, Van Lente F, Wang S and the AASK Study Group. Low rates of adequate lipid management in African Americans with or at risk for renal disease. American Society of Nephrology 32nd Annual Meeting, Miami Beach, Florida, November 5-8, 1999.

Pogue V, Bakris G, Cheek D, Greene T, Lea J, Randall O, Toto R and the AASK Study Group. Association of pulse pressure with glomerular filtration rate: A cross-sectional study of 2037 African Americans. American Society of Nephrology 32nd Annual Meeting, Miami Beach, Florida, November 5-8, 1999.

Douglas JG. Recruitment of African Americans in NIH Funded Clinical Trials: AASK Design, Demographics and BP Control. Jackson Heart Symposium, Jackson, Mississippi, May 3, 2000.

Lea JP, Appel U, Douglas JG, Faulkner M, Kopple ID, Lightfoot T, Zhang W for the AASK Study. Nutritional factors and their relationship to renal function in African American patients with hypertensive renal disease. American Society of Nephrology 32nd Annual Meeting, Toronto, Canada, October 13-16, 2000.

Lipkowitz MS. Agodoa L, Bakris G, Dowie D, Greene T, Jaen L, Middleton J and the AASK Study Group. Relationship between uric acid and blood pressure renal disease and cardiovascular disease in African American Study of Kidney Disease and Hypertension (AASK) patients. American Society of Nephrology 32nd Annual Meeting, Toronto, Canada, October 13-16, 2000.

Douglas JG, Thornley-Brown D, Ojo A, Pogue V, Rahman M, Randall O, Wright JT, Zhang W for the AASK Study Group. Ramipril and amlodipine-based therapy in the African American Study of Kidney Disease and Hypertension (AASK): Supplemental drugs and side effects. 14th International Interdisciplinary Conference on Hypertension in Blacks, Las Vegas, Nevada, July 8-12, 2001.

Lea JP, Hiremath L, Kopple JD, Toto RD, Wang S-R from the AASK Study. Dietary sodium intake is associated with the degree of proteinuria in African-Americans with hypertensive renal disease. 14th International Interdisciplinary Conference on Hypertension in Blacks, Las Vegas, Nevada, July 8-12, 2001.

Miller ER, Appel U, Cheek D, Gassman JJ, Kusek JW, Lash J, Schulman G from the AASK Study. Effects of ramipril-and amlodipine-based therapy on proteinuria: Results from the African American Study of Kidney Disease (AASK). 14th International Interdisciplinary Conference on Hypertension in Blacks, Las Vegas, Nevada, July 8-12, 2001.

Norris K, Agodoa L, Douglas M, Gayle R, Greene T, Lea J, Wright J from the AASK Study. Renal outcome differences between ACE inhibitor and dihydropyridine calcium

antagonist based treatment of hypertensive renal disease. 14th International Interdisciplinary Conference on Hypertension in Blacks, Las Vegas, Nevada, July 8-12, 2001.

Phillips R, Agodoa L, Bakris G, Douglas J, Lewis J, Middleton J, Wang S-R from the AASK Study Group. Predictors of multiple drug therapy in the African American Study of Kidney Disease and Hypertension (AASK). 14th International Interdisciplinary Conference on Hypertension in Blacks, Las Vegas, Nevada, July 8-12, 2001.

Lash JP, Agodoa L, Brittain K, Cheek D, Contreras G, Gassman J, Miller ER, Randall O, Thornley-Brown D and the AASK Study Group. ACE-inhibitors and calcium channel blockers are safe and well tolerated in patients with chronic renal insufficiency: Interim results of the AASK Study. 2001 ASN/ISN World Congress of Nephrology, San Francisco, California, October 12-17, 2001.

Lea JP, Contreras G, Kopple JD, Schulman G, Wang S-R, Lightfoot T, Richardson A and the AASK Study Group (AASK). The use of diuretic therapy in achievement of blood pressure goals in the African-American Study of Kidney Disease and Hypertension (AASK). 2001 ASN/ISN World Congress of Nephrology, San Francisco, California, October 12-17, 2001.

Middleton J, Agodoa L, Douglas J, Lewis J, Lipkowitz M, Littmon L, Randall OT, Zhang W and the AASK Study Group. Reversibility of initial acute GFR response to dihydropyridine calcium channel blocker in hypertensive nephrosclerosis in the African American Study of Kidney Disease and Hypertension (AASK). 2001 ASN/ISN World Congress of Nephrology, San Francisco, California, October 12-17, 2001.

Miller ER III, Appel U, Cheek D, Greene T, Kusek JW, Lash J, Schulman G and the AASK Study Group (AASK). Ramipril and amlodipine-based therapy to prevent proteinuria: Results from the African American Study of Kidney Disease (AASK). 2001 ASN/ISN World Congress of Nephrology, San Francisco, California, October 12-17, 2001.

Norris K, Agodoa L, Douglas M, Gayle R, Greene T, Lea J, Wright J. Differences in renal outcomes between ACE inhibitor and dihydropyridine calcium channel blocker persist after adjustment for blood pressure and add-on drugs for hypertensive kidney disease. 2001 ASN/ISN World Congress of Nephrology, San Francisco, California, October 12-17, 2001.

Appel U, Bakris G, Douglas-Baltimore J, Greene T, Kopple J, Massry S, Wang X for the AASK Research Group. The relationship between achieved blood pressure and renal outcomes in the African American Study of Kidney Disease (AASK). American Society of Nephrology $_{35}$th Annual Meeting, Philadelphia, Pennsylvania, October 30-November 4, 2002.

Lea J, Bakris G, Greene T, Hebert L, Lipkowitz M, Massry S, Middleton J, Miller E, Rostand S, Smith W for the AASK Study Group. Association of baseline proteinuria and GFR with progression of kidney disease in the African American Study of Kidney Disease (AASK). American Society of Nephrology 35th Annual Meeting, Philadelphia, Pennsylvania, October 30-November 4, 2002.

Lewis J, Greene T, Appel L, Contreras G, Douglas J, Lash J, Toto R, Van Lente F, Wright J for the AASK Study Group. Effects of interventions on outcomes based on serum creatinine in the African American Study of Kidney Disease (AAS K). American Society of Nephrology 35th Annual Meeting, Philadelphia, Pennsylvania, October 30-November 4, 2002.

Middleton J for the AASK Study Group. Renal outcomes in the context of an acute GFR effect of dihydropyridine CCBs in the African American Study of Kidney Disease (AASK). American Society of Nephrology 35th Annual Meeting, Philadelphia, Pennsylvania, October 30-November 4, 2002.

Miller ER, III, Appel U, Wang S, Bakris GL, Hebert L, Lipkowitz M, Massry S, Middleton J, Rostand S, Smith W for the AASK Study Group. The effect of different blood pressure goals and antihypertensive drug regimes on change in proteinuria: Results from the African American Study of Kidney Disease. American Society of Nephrology 35$^{th}$ Annual Meeting, Philadelphia, Pennsylvania, October 30-November 4, 2002.

*aask.docs/proj/l:/Publications/presentationl2O2.doc*

# Appendix J. AASK Manuscript Writing Committees and Status October 2002

#1 - Design and Statistical Aspects of the AASK Study
Rejected by Controlled Clinical Trials

Jennifer Gassman, Ph.D. - DCC, *Chair*
Lawrence Y. Agodoa, M.D. - NIH-NIDDK
Gerald Beck, Ph.D. - DCC
Janice Douglas, M.D. - Steering Committee Chair
Tom Greene, Ph.D. - DCC
Michael Kutner, Ph.D. - DCC
Shin-Ru Wang, M.S. - DCC
Jackson T. Wright, Jr., M.D., Ph.D. — CWRU/University Hospitals of Cleveland

#3 - Blood Pressure/Cardiovascular Risk Factors in Screenees
On Hold

DeAnna Cheek, M.D. - Medical University of South Carolina, *Chair*
George L. Bakris, M.D. - Rush-Presbyterian-St. Luke's Medical Center
Jacques J. Bourgoignie, M.D. - University of Miami
William Cleveland, M.D. - Morehouse School of Medicine
John Kusek, Ph.D. - NIH-NIDDK
Shaul Massry, M.D. - University of Southern California
Keith Norris, M.D. - MLK/Drew Medical Center
Velvie Pogue, M.D. - Harlem Hospital Center
Tamarat Retta, M.D., Ph.D. - Howard University
Shin-Ru Wang, M.S. - DCC

#5- Recruitment Strategies for AASK Patients
Draft Written

Robert Phillips, M.D., Ph.D. - Mount Sinai Medical Center/Lenox Hill Hospital, *Chair*
Marquetta Faulkner, M.D. - Meharry Medical College
Jennifer Gassman, Ph.D. - DCC
Luzmaria Jaen, R.N. - Case Western Reserve University
John Kusek, Ph.D. - NIH-NIDDK
Tammy Lightfoot, R.N. - University of Southwestern Texas
Keith Norris, M.D. – MLK/Drew School of Medicine
Akinlou Ojo, M.D. - University of Michigan
Annie Richardson, L.V.N. - University of Southern California
Robert Thompson, P.A.C. - University of Florida

*Current AASK Writing Committees (cont'd)*

#6- Association of Quality of Life and Renal Function
Draft Written

Stephen G. Rostand, M.D. - University of Alabama, *Chair*
George L. Bakris, M.D. - Rush-Presbyterian-St. Luke's Medical Center
Gerald Beck, Ph.D. - DCC
Jeanne Charleston, R.N. - Johns Hopkins University
Tom Greene, Ph.D. - DCC
Yvette Hall, R.N. - Case Western Reserve University
Leroy Herbert, M.D. - Harlem Hospital Center
John Kusek, Ph.D. - NJH-NIDDK
Mark Unruh, M.D. - NEMC
Michael Rocco, M.D. - Wake Forest University Medical Center
Weihong Zhang, M.S. - DCC

#8- Predictors of MAP Separation
On Hold

Paul Greene, Ph.D. - University of Alabama, *Co-Chair*
Leena Hiremath, Ph.D. - Ohio State University, *Co-Chair*
George L. Bakris, M.D. - Rush-Presbyterian-St. Luke's Medical Center
Gabriel Contreras, M.D. - University of Miami
Tom Greene, Ph.D. - Data Coordinating Center
John Kusek, M.D. - National Institutes of Health
John Middleton, M.D. - University of Texas SW Medical Center
Keith Norris, M.D. - Martin Luther King-Drew Medical College
Mahboob Rahman, M.D. - Case Western Reserve University
Annie Richardson, L.V.N. - University of Southern California

#11 - Low Rates of Adequate Lipid Management
Draft Written

Robert Phillips, M.D., Ph.D. - Mount Sinai Medical Center/Lenox Hill Hospital, *Chair*
Crystal Gadegbku, M.D. - Medical University of South Carolina
James Lash, M.D. - Rush-Presbyterian-St. Luke's Medical Center
John Middleton, M.D. - University of Texas SW Medical Center
Stephen G. Rostand, M.D. - University of Alabama
Frederick Van Lente, Ph.D. - Central Biochemistry Laboratory
Shin-Ru Wang, M.S. - DCC

*Current AASK Writing Committees (cont'd)*

#13 - Ethical Considerations in Patient Retention

Deborah Brooks, M.S.N., R.N. - Medical University of South Carolina, *Chair*
Jeanne Charleston, R.N. - John Hopkins University
Donna Dowie, M.D. - Harlem Hospital Center
Avril B. Gabriel, R.N., MPA — Lenox Hill Hospital
Yvette Hall, R.N. - Case Western Reserve University
Leena Hiremath, Ph.D. - Ohio State University
Tammy Lightfoot, R.N. - University of Texas Southwestern Medical Center at Dallas
Carolyn Johnson, R.N. - University of Alabama
Mohammed Sika, Ph.D. - Vanderbilt University
Winifred Smith, M.P.H. - Morehouse School of Medicine

**FOLLOW-UP PAPERS WAITING TO START:**

#14 - Baseline Predictors of Progression of Renal Disease

Keith Norris, M.D. - Martin Luther King Drew Medical College, *Chair*
Tom Greene, Ph.D. - DCC
Joel Kopple, M.D. - Harbor-UCLA Medical Center
Janice Lea, M.D. - Emory University
Julie Lewis, M.D. - Vanderbilt University
Michael Lipkowitz, M.D. - Mount Sinai Medical Center
Pete (Edgar) R. Miller, M.D., Ph.D. - John Hopkins University
Annie Richardson, L.V.N. - University of Southern California
Stephen G. Rostand, M.D. - University of Alabama
DCC Rep.

#15 - Acute Effect

John Middleton, M.D. - University of Texas SW Medical Center at Dallas, *Chair*
Lawrence Y. Agodoa, M.D. – NlDDK/National Institutes of Health
George L. Bakris, M.D. - Rush-Presbyterian-St. Luke's Medical Center
Francis Gabbal, M.D. - University of California, San Diego
Mahboob Rabman, M.D. - Case Western Reserve University
Stephen G. Rostand, M.D. - University of Alabama
C. Cralg Tisher, M.D. - University of Florida
DCC Rep.

*Current AASK Writing Committees (cont'd)*

#16 - Mechanistic Analysis of Changes in Proteinuria and Changes in Renal Function

George L. Bakris, M.D. - Rush-Presbyterian-St. Luke's Medical Center, *Chair*
Tom Greene, Ph.D. - DCC
Lee Hebert, M.D. - Ohio State University
Michael Lipkowitz, M.D. - Mount Sinai School of Medicine
Shaul Massry, M.D. - University of Southern California
John Middleton, M.D. - University of Texas SW Medical Center at Dallas
Pete (Edgar) R. Miller, M.D., Ph.D. — John Hopkins University
Winifred Smith, M.P.H. - Morehouse School of Medicine

#17 - Renal Function Outcomes

Tom Greene, Ph.D. - DCC, *Co-Chair*
Julie Lewis, M.D. - Vanderbilt University, *Co-Chair*
Jackson T. Wright, Jr., M.D., Ph.D.-CWRU/University Hospitals of Cleveland, *Co Chair*
Lawrence J. Appel, M.D., M.P.H. - John Hopkins University
Gabriel Contreras, M.D. - University of Miami
Janice Douglas, M.D. - Steering Committee Chair
Jim Lash, M.D. - Rush-Presbyterian-St. Luke's Medical Center
Robert Toto, M.D. - University of Texas SW Medical Center at Dallas
Frederick Van Lente, Ph.D. - Central Biochemistry Laboratory

#18 - Adherence as Predictor of Outcomes

Joel Kopple, M.D. - Harbor-UCLA Medical Center, *Chair*
Jeanne Charleston, R.N. - John Hopkins University
Donna Dowie, M.D. - Harlem Hospital Center
Tammy Lightfoot, R.N. - University of Texas SW Medical Center at Dallas
Tamarat Retta, M.D., Ph.D. - Howard University
Leene Hiremath, Ph.D. - Ohio State University
DCC Rep.
NIH Rep.

#19 LVH and Its Relationship to Drug Regimens, BP and Outcomes

Michael Lipkowitz, M.D. - Mount Sinai Medical Center, *Chair*
James Lash, M.D. - Rush-Presbyterian-St. Luke's Medical Center
Robert Phillips, M.D., Ph.D. - Mount Sinai School of Medicine/Lenox Hill Hospital
Otelio S. Randall, M.D. - Howard University
Stephen G. Rostand, M.D. - University of Alabama
Current AASK Writing Committees (cont'd)

*Current AASK Writing Committees (cont'd)*

Gerald Schulman, M.D. - Vanderbilt University
DCC Rep.
NIH Rep.

#20 - Achieved Blood Pressure

Lawrence J. Appel, M.D., M.P.H. - John Hopkins University, *Chair*
George L. Bakris, M.D. - Rush-Presbyterian-St. Luke's Medical Center
Janice Douglas, M.D. - Steering Committee Chair
Joel Kopple, M.D. - Harbor-UCLA Medical Center
Shaul Massry, M.D. - University of Southern California
Gerald Schulman, M.D. - Vanderbilt University
DCC Rep.
NIH Rep.

#21 - Pulse Pressure and Its Relationship to Outcomes

Otelio S. Randall, M.D. - Howard University, *Chair*
Kenneth Jamerson, M.D. - University of Michigan
Keith Norris, M.D. - Martin Luther King-Drew Medical College
Velvie Pogue, M.D. - Harlem Hospital Center
Shichen Xu, M.D. - Howard University
DCC Rep.
NIH Rep.

#22 - Quality of Life and Its Relationship to BP, Drug Medications

James Lash, M.D. - Rush-Presbyterian-St. Luke's Medical Center, *Chair*
Janice Douglas, M.D. - Steering Committee Chair
Crystal Gadegbeku, M.D. - Medical University of South Carolina
Yvette Hall, R.N. - Case Western Reserve University
Kim Jones, B.S. - University of Texas SW Medical Center at Dallas
John Kusek, Ph.D. - NIH-NIDDK
Mohammed Sika, Ph.D. - Vanderbilt University
DCC Rep.

#23 - New Onset Diabetes and Its Relationship with Drug Medications, Proteinuria, BMI, etc.

DeAnna Cheek, M.D. - Medical University of South Carolina, *Chair*
Lawrence Y. Agodoa, M.D. - NIH-NLDDK
Denyse Thornley-Brown, M.D. - University of Alabama
Gabriel Contreras, M.D. - University of Miami
Current AASK Writing Committees (cont'd)

Jennifer Gassman, Ph.D. - DCC
Jim Lash, M.D. - Rush-Presbyterian-St. Luke's Medical Center
Pete (Edgar) R. Miller, M.D., Ph.D. - John Hopkins University
Otelio S. Randall, M.D. - Howard University

#24 - Management of Pre-ESRD Patients

DeAnna Cheek, M.D. - Medical University of South Carolina, *Chair*
Lawrence Y. Agodoa, M.D. - NIH-NLDDK
Deborah Brooks, M.S.N., R.N. - Medical University of South Carolina
Denyse Thornley-Brown, M.D. - University of Alabama
Gabriel Contreras, M.D. - University of Miami
Jennifer Gassman, Ph.D. - DCC
Jim Lash, M.D. - Rush-Presbyterian-St. Luke's Medical Center
Janice Lea, M.D. - Emory University
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Otelio S. Randall, M.D. - Howard University

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